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Archives of Internal Medicine

VOLUME 48 OCTOBER, 1931 NUMBER 4

# THE TREATMENT FOR SECONDARY ANEMIA

## A STUDY OF THE RESULTS IN ONE HUNDRED AND TWENTY-SIX CASES *

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AND
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Classification of the Anemias
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The Response of the Reticulocytes
Summary and Conclusions

For the past two years, we have been engaged in a study of the various forms of anemia that were observed in patients admitted to

* Submitted for publication, Jan. 24, 1931.
* From the Department of Medicine, Peiping Union Medical College.

the general medical wards of the Peiping Union Medical College. The purpose of these observations was to study the course of the blood following various forms of treatment and to obtain information regarding the factors that influence the regeneration of hemoglobin in man. We were aware of the difficulties in drawing conclusions following various forms of treatment because of the many variable factors present in different patients, and it also was evident that many of the factors could not be evaluated quantitatively. In any study of the cause of anemia one usually considers such conditions as loss of blood, the previous diet of the patient, the presence of infection, the reserve supply of materials necessary for the formation of hemoglobin, the function of the bone marrow, the evidences of increased destruction of blood and the total volume of the blood. In many instances it is difficult and sometimes impossible to evaluate the relative importance of each

TABLE 1.—*Forms of Anemia Studied*

| Type | | | | Number of Cases |
|---|---|---|---|---|
| Posthemorrhagic anemia | | | | 15 |
| Dysentery | | | | 20 |
| Malnutrition | | | | 17 |
| Pregnancy | | | | 9 |
| Hookworm | | | | 7 |
| Kala-azar | | | | 28 |
| Miscellaneous cases | | | | 30 |
| Malaria | 3 | Pernicious anemia | 2 | |
| Chlorosis | 4 | Syphilis | 3 | |
| Splenic anemia | 4 | Typhoid fever | 1 | |
| Anemia following splenectomy | 2 | Cirrhosis of liver | 1 | |
| Chronic nephritis | 1 | Acute leukemia | 1 | |
| Tuberculosis of intestines | 4 | Purpura hemorrhagica | 1 | |
| Aplastic anemia | 2 | Cancer of stomach | 1 | |
| Total number of cases | | | | 126 |

factor. However, by studying each patient before and after treatment and comparing the results under similar conditions, valuable information may be obtained. In this paper we present the results of a study of 126 patients with anemia.

## CLASSIFICATION OF THE ANEMIAS

We did not classify our cases on a basis of the morphologic characteristics of the blood, nor according to the more general classifications such as anemias due to increased destruction or defective formation of the blood, but we divided them into groups according to the condition with which the anemia was associated, and the various factors contributing to the production of the anemia were analyzed. Thus, the anemia associated with chronic dysentery was studied from the point of view of loss of blood, the previous diet of the patient, the presence of infection, changes in gastric secretion and the nutritional disturbances caused by the diarrhea. In this way, the various factors precipitating the development of anemia were evaluated. The various forms of anemia studied are summarized in table 1.

## METHODS OF STUDY

All of the patients were studied while resident in the hospital and were observed for periods of time varying between twenty-one and one hundred and twenty days. They were examined carefully for evidence of loss of blood, and all of the clinical features were noted. The red blood cells were counted with standardized counting chambers and pipets, and the hemoglobin content was determined by the Sahli method in which a colored glass was used for the standard. This instrument was calibrated with the oxygen capacity method so that 100 per cent was equal to 17 Gm. of hemoglobin or an oxygen capacity of 22.5 per cent by volume. The reticulocytes were counted, the dry smear technic being used. All of these determinations were made in the different patients at intervals varying from one to four days. The morphologic characteristics of the blood were studied, and the presence of nucleated erythrocytes and the changes in the size and shape of the cells were noted. In a number of the cases the exact size of the erythrocytes was measured with a calibrated ocular micrometer, and the Price-Jones curves were plotted.

In evaluating the results of treatment, the rate of the formation of hemoglobin was determined before and after treatment, and the reticulocytes were followed daily. In this way it was possible to reach a conclusion regarding the value of the treatment employed.

## SPECIAL CLINICAL FEATURES

Before summarizing the results of the study of the blood, we wish to call attention to a number of the interesting clinical features that were observed. We refer to changes in the tongue, skin, ocular fundi, nervous system and gastric acidity, together with other complicating conditions, such as the various deficiency disorders due to avitaminosis and other nutritional defects.

*Changes in the Tongue.*—Atrophy of the papillae of the tongue was observed in nine patients. The degree of atrophy varied from a disappearance of the papillae in the central portion of the tongue to complete atrophy of all of the papillae. Following recovery from the anemia, the papillae returned and the tongue appeared normal. The natural history of this phenomenon is unknown since it was asymptomatic in all but one patient. In this man, the atrophy had been preceded by recurrent attacks of glossitis. The picture presented by the tongue was indistinguishable from that frequently seen in pernicious anemia. Besides these cases, we have observed atrophy of the papillae of the tongue in three other patients who had chronic dysentery without anemia.

Aside from the conditions mentioned, atrophy of the papillae of the tongue may be observed in sprue, pellagra, dysphagia associated with

anemia, and following gastrectomy, and also in some patients with anemia associated with a chronic infestation due to hookworm. While its exact significance is difficult to appreciate, these changes are usually present in patients who are undernourished or who have a pathologic process that interferes with nutrition. It may be added that these conditions may be present without gastric anacidity.

*Changes in the Skin.*—The lesions of the skin that are characteristic of pellagra were present in two patients and hyperkeratosis folliculosis in three. The latter condition was extensive, and presented an extraordinary clinical picture. Frazier and Hu [1] made a special study of this condition and attributed these changes to deficiency in vitamin A; they reported the results of their investigations in detail elsewhere. All of these lesions disappeared following the recovery from anemia and establishment of an adequate diet.

*Retinal Hemorrhages.*—Hemorrhages into the retina are observed commonly in patients with pernicious anemia, in the anemias associated with hemorrhagic phenomena and in chronic nephritis, but they are uncommon in other forms of anemia. In the cases that we studied, numerous hemorrhages were present in the retinas of four patients. In three, the anemia was associated with chronic dysentery, and in one, it resulted from bleeding hemorrhoids. In all, the erythrocyte count was less than 1,500,000 cells. The hemorrhages were associated with patches of exudation which resembled those seen in patients with retinal vascular changes. It seemed to us that the appearance of hemorrhage in the eyegrounds depended on the severity of the anemia rather than its cause. Heine [2] called attention to the hemorrhages occurring in the ocular fundi in the various anemias in man, and stated that this condition is more common in pernicious anemia than in other forms of anemia.

*Changes in the Nervous System Associated with Anemia.*—Changes in the nervous system were present in seven patients. In five, the clinical observations were characteristic of subacute combined degeneration. In two of these, typical pernicious anemia was present. Of the other three cases, two were associated with chronic dysentery, and the third was present in a woman with gastric anacidity and anemia resulting from loss of blood. Gastric anacidity was present in all of the five patients, but in one patient in whom the signs were associated with anemia and chronic dysentery, the gastric anacidity was only temporary.

1. Frazier, C. N., and Hu, C. H.: Hyperkeratosis Follicularis: Preliminary Report, Tr. International Dermatological Conference, Stockholm, 1930.

2. Heine, L.: Die Krankheiten des Augen, Berlin, Julius Springer, 1921, p. 392.

Peripheral neuritis was observed twice. In both cases, it was associated with anemia and chronic dysentery, but it was unassociated with gastric anacidity.

It was striking that these maladies were present in patients who had nutritional defects; and the isolated observation of the presence of subacute combined sclerosis in a patient with anemia and a temporary derangement of gastric function is of interest in view of the relationship existing between gastric anacidity, subacute combined sclerosis and nutritional defects.

The development of peripheral neuritis in association with chronic dysentery and anemia was of interest from the standpoint of etiologic diagnosis. The questions naturally arose: Was the peripheral neuritis due to deficiency in vitamins, so-called beriberi, or was it the result of the dysenteric infection? At present we do not know of any method of answering these questions conclusively. In the future, similar cases should be studied from the point of view of a deficiency disorder being the cause of neuritis.

*Changes in Gastric Secretion.*—It is becoming clearer that alterations in gastric secretory function are of considerable importance in predisposing many patients to the development of pernicious anemia. This belief is due to the recent important work of Castle and his associates, Townsend and Heath.[3] They have been able to demonstrate conclusively that in patients with gastric anacidity and pernicious anemia, the stomach is incapable of secreting a substance (an intrinsic factor, possibly an enzyme) that is present in normal human gastric juice and is capable of interaction with protein or closely related substances, resulting in the production of material having a marked hematopoietic effect when administered to patients with pernicious anemia. Moreover, Castle and his co-workers have shown that some patients with achlorhydria and anemia may be able to secrete this substance, whereas in these patients the stomachs do not secrete hydrochloric acid; and they have also observed patients with an anemia closely simulating the blood picture of pernicious anemia, who were capable of secreting hydrochloric acid, but in whom the gastric juice was ineffective when tested for its ability

3. Castle, W. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: I. The Effect of the Administration to Patients with Pernicious Anemia of the Contents of the Normal Human Stomach Recovered After the Ingestion of Beef Muscle, Am. J. M. Sc. **178**:748, 1929. Castle, W. B., and Townsend, W. C.: II. The Effect of the Administration to Patients with Pernicious Anemia of Beef Muscle After Incubation with Normal Human Gastric Juice, ibid., p. 764. Castle, W. B.; Townsend, W. C., and Heath, C. W.: III. The Nature of the Reaction Between Normal Human Gastric Juice and Beef Muscle Leading to Clinical Improvement and Increased Blood Formation Similar to the Effect of Liver Feeding, ibid. **180**:305, 1930.

to produce the effective principle from beef muscle. These observations not only explain why anemia does not develop in some patients with gastric anacidity but they may also explain why pernicious anemia does not develop in many patients with anacidity, and why it develops in some patients with normal gastric acidity.

It is clear, then, that alterations in gastric secretory function are of importance in the study of any form of anemia. When the gastric secretory function of patients with anemia is studied repeatedly, histamine being used as a test stimulus, two types of response are observed:[4] a permanent type of gastric anacidity, or a temporary suppression of "free" acid. In the group under discussion, the gastric secretion of sixty-five patients was studied and gastric anacidity was found in sixteen. In six, it was only temporarily present; in two, there was typical pernicious anemia; and of the remaining eight, only three were examined more than once. We were unable to establish any definite correlation between gastric anacidity and anemia in most of our patients. However, a final answer to the question of the relationship between various forms of anemia other than pernicious anemia and alterations in gastric function cannot be given at the present time.

*Association with Deficiency Disorders.*—One of the interesting features in some of the patients observed was the evidence of deficiency disorders, such as keratomalacia, scurvy, osteomalacia, rickets and "edema disease." We observed keratomalacia in five, edema in ten, rickets in two, scurvy in two and osteomalacia in one. In a previous paper, we[5] pointed out that deficiency disorders such as keratomalacia, beriberi, rickets, scurvy, osteomalacia and tetany may be present without anemia, and if anemia is present in such patients it was concluded that it was due to a deficiency of substances other than vitamins A, B, C and D, or to some complicating factor such as infection. These conclusions were based on a study of the blood in twenty-two cases of keratomalacia, forty-one cases of beriberi, four cases of scurvy, seventeen cases of rickets, thirteen cases of osteomalacia and twenty-two cases of tetany resulting from pregnancy, lactation or a deficient diet. Anemia associated with edema will be discussed under the anemias associated with undernutrition.

*Rarity of Pernicious Anemia.*—During this study we observed only a single typical case of pernicious anemia in a Chinese patient. It has been the experience of all clinicians who have had an opportunity of

4. Chang, H. C.; Yang, C. S., and Keefer, C. S.: Improvement in Gastric Function in Patients Following Recovery from Secondary Anemia, Nat. M. J., China **15**:752, 1929.

5. Keefer, C. S., and Yang, C. S.: The Rôle of the Various Vitamines in the Production of Anemia, Nat. M. J., China **15**:419, 1929.

studying anemia in Chinese patients to note the infrequency of pernicious anemia. In the clinical records of the first 25,000 patients admitted to the Peiping Union Medical Hospital there were notes of only four cases in which a diagnosis of pernicious anemia seemed justified, and all but one of these were observed before treatment with liver was known. Fu and Sturton,[6] Morris[7] and Struthers[8] observed some cases, but details are lacking. Dr. George R. Minot informed us that he observed two typical cases in Chinese patients in America. The reason for the uncommon occurrence of the disease is not clear. There are two suggestive points. In a study of the gastric contents of patients in whom histamine was used as a test stimulus, Chang[9] showed that gastric anacidity was present in only 7.5 per cent of the cases studied.

TABLE 2.—*Results of Treatment for Posthemorrhagic Anemia*

| | Red Blood Cells, Millions | | Hemoglobin, per Cent | | Reticulocytes, per Cent | | |
|---|---|---|---|---|---|---|---|
| Case | Before Treatment | After Treatment | Before Treatment | After Treatment | Before Treatment | After Treatment | Types of Treatment |
| 1 | 3.0 | 5.0 | 45 | 85 | 0 | 3.5 | Transfusion |
| 2 | 4.25 | 5.0 | 50 | 85 | 0 | 7.0 | Transfusion |
| 3 | 3.5 | 3.75 | 50 | 75 | 0 | 8.0 | Transfusion |
| 4 | 1.25 | 3.75 | 20 | 65 | 0 | 2.0 | Transfusion |
| 5 | 2.5 | 4.0 | 30 | 55 | 0 | 1.0 | Iron |
| 6 | 4.7 | 5.7 | 52 | 75 | 0 | 7.5 | Iron |
| 7 | 2.25 | 4.75 | 35 | 90 | ... | ... | Liver and iron |
| 8 | 3.0 | 5.0 | 25 | 85 | 0 | 1.5 | Liver and iron |
| 9 | 4.9 | 5.18 | 50 | 80 | 0.4 | 6.6 | Liver and iron |
| 10 | 3.08 | 4.0 | 42 | 72 | 0.2 | 4.8 | Liver and iron |
| 11 | 1.02 | 4.35 | 13 | 80 | 15.0 | 8.0 | Liver; iron |
| 12 | 3.46 | 5.89 | 43 | 102 | 0.8 | 5.0 | Liver, iron and liver |
| 13 | 1.42 | 4.34 | 22 | 70 | 1.8 | 12.0 | Liver and iron |
| 14 | 2.65 | 3.83 | 31 | 49 | 1.4 | 1.2 | Liver extract |
| 15 | 1.75 | 2.35 | 33 | 38 | 3.6 | 2.4 | Liver extract |

While it is difficult to compare these results with those obtained from a similar group in the United States, owing to the method employed, it is suggested that the incidence of gastric anacidity in a miscellaneous group of hospitalized patients may be lower in China than elsewhere. Moreover, the difference in the dietary habits of oriental and occidental people may be of importance in explaining the infrequency of pernicious anemia in China. Both of these questions require further investigation.

## VARIOUS GROUPS OF ANEMIA

*Posthemorrhagic Anemia.*— We have studied fifteen patients with posthemorrhagic anemia, and the results of treatment are summarized in table 2. The most conspicuous results were obtained following the

6. Fu, W., and Sturton, S. D.: A Severe Case of Pernicious Anemia, China M. J. **40**:1016, 1926.

7. Morris, H. H.: Anemias in China, China M. J. **43**:768, 1929.

8. Struthers, G., in discussion on Morris (footnote 7).

9. Chang, H. C.: Personal communication to the authors.

administration of liver and iron. Chart 1 illustrates such a case. Similar observations have been recorded by Minot, Murphy and Stetson,[10] Murphy and Powers,[11] Dyke,[12] Vaughan,[13] Wahlberg,[14] and others.

In drawing conclusions from the results of the treatment of patients with this form of anemia, there are difficulties due to the varying response observed following treatment. For example, it is generally

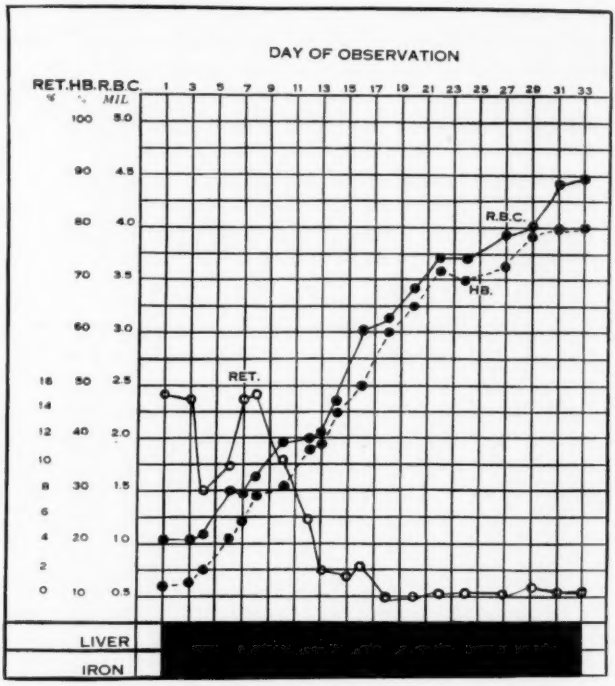


Chart 1.—Chart of patient with anemia resulting from chronic loss of blood. Recovery was rapid after treatment with liver and iron. The reticulocytes were increased before treatment was started.

10. Minot, G. R.; Murphy, W. P., and Stetson, R. P.: The Response of the Reticulocytes to Liver Therapy in Pernicious Anemia, Am. J. M. Sc. **175**:581, 1928.

11. Murphy, W. P., and Powers, J. H.: The Value of Liver in the Treatment of Anemia Due to Hemorrhage, Surg., Gynec. & Obst. **48**:480, 1929.

12. Dyke, S. C.: Liver Therapy in Secondary Anemia, Lancet **1**:1192, 1929.

13. Vaughan, Janet: Critical Review: The Liver Treatment of Anemias, Quart. J. Med. **23**:213, 1930.

14. Wahlberg, J.: Liver Diet and Reticulocyte Reaction in Simple Anemia, Acta med. Scandinav. **72**:143, 1929.

believed that the period of recovery following an acute hemorrhage is relatively rapid; that is to say, complete recovery may occur within several weeks after the hemorrhage regardless of treatment. This has been shown to be true in the experimental posthemorrhagic anemias in animals and in similar anemias in man. This rapid recovery is due to the presence of a large amount of reserve material which is available for the regeneration of the red cells, and the hemoglobin. There are patients, however, who continue to have anemia for many weeks following an acute hemorrhage, and recovery may be slow. Such cases have been reported by Dyke,[12] and we have observed similar cases. In these patients the reserve supply of hemoglobin and red cell substances must be small. This view gains support in the experimental work of McCay,[15] who was able to show that animals recovering from a posthemorrhagic anemia might be rendered anemic by a relatively small bleeding, whereas the loss of a similar amount of blood from an animal which had not been anemic previously was not followed by anemia. These observations emphasize the importance of an adequate reserve supply of the substances that build hemoglobin in determining the appearance of anemia and the rate of recovery following acute hemorrhage.

On the other hand, the chronic posthemorrhagic anemias usually present an entirely different problem. In such cases, the reserves have usually been exhausted, and if the materials necessary for regeneration of the blood are not supplied in large quantities in the diet, the rate of recovery will be slow. Whipple and Robschiet-Robbins were the first to emphasize the importance of dietetic therapy in the treatment for this form of anemia. When their dogs had chronic anemia from repeated bleeding, the hemoglobin content of the blood could be maintained at a surprisingly low level for several years, providing the diet was not made up of large amounts of food containing the materials necessary for the regeneration of hemoglobin. They found that liver and kidney contained the largest amount of these substances, but iron and the salts of other metals were also potent. They pointed out that liver and iron produced an effect of the two expected reactions. It is not surprising, therefore, that a similar response may be observed in those anemias in man that are caused by bleeding. It should be emphasized that complete recovery may not occur in less than from four to six weeks in these patients, even following the administration of liver and iron; but this result is as satisfactory as that observed in some patients with pernicious anemia following the use of liver extract, and

15. McCay, C. M.: The Influence of Protein, Blood, Liver, Fat, Iron, and Potassium in the Diet upon the Rate of Blood Regeneration After Hemorrhage in the Rat and Dog, Am. J. Physiol. **84**:16, 1928.

recovery is usually considerably more rapid than that observed when these patients recover without such treatment.

It is manifest, therefore, that recovery from posthemorrhagic anemia may be accelerated by the use of liver and iron, provided such inhibitory factors as sepsis and continual loss of blood are not present.

*Anemias Associated with Undernutrition.*—In a previous paper we[16] reported cases of anemia resulting from malnutrition. The anemia was caused either by faulty diets, or by pathologic processes interfering with normal nutrition, such as chronic diarrhea. Since that time,

TABLE 3.—*Anemia of Malnutrition*

| Case | Red Blood Cells, Millions | | Hemoglobin, per Cent | | Reticulocytes, per Cent | | Type of Treatment | Comment |
|---|---|---|---|---|---|---|---|---|
| | Before Treatment | After Treatment | Before Treatment | After Treatment | Before Treatment | After Treatment | | |
| 36 | 2.68 | 4.34 | 44 | 80 | 0.8 | 6.3 | Diet | Typhus |
| 37 | 3.08 | 3.99 | 56 | 82 | 3.0 | 7.0 | Diet | Edema |
| 38 | 3.25 | 5.0 | 60 | 85 | ... | 2.0 | Diet | Osteomalacia |
| 39 | 2.5 | 4.75 | 45 | 85 | ... | 3.0 | Diet | Scurvy |
| 40 | 3.40 | 4.70 | 53 | 87 | 0.8 | 13.2 | Diet | Edema |
| 41 | 3.16 | 4.02 | 59 | 80 | 5.6 | 4.6 | Diet | Edema |
| 42 | 3.00 | 5.41 | 33 | 97 | 0.6 | 4.4 | Iron | |
| 43 | 38.9 | 4.92 | 44 | 75 | 0.6 | 9.0 | Iron | Edema |
| 44 | 3.00 | 4.98 | 58 | 89 | 3.2 | 5.0 | Iron | Edema |
| 45 | 2.84 | 3.81 | 43 | 63 | 0.2 | 9.8 | Liver and iron | Keratomalacia |
| 46 | 2.84 | 4.49 | 39 | 83 | 0.2 | 10.0 | Liver and iron | |
| 47 | 1.47 | 3.81 | 18 | 73 | 7.0 | 17.4 | Liver and iron | Keratomalacia |
| 48 | 1.84 | 4.36 | 26 | 85 | 0.0 | 13.0 | Liver and iron | |
| 49 | 0.69 | 5.25 | 17 | 90 | 0.2 | 35.8 | Liver extract | In childhood |
| 50 | 3.00 | 5.25 | 52 | 85 | 6.0 | 0.0 | Liver extract | In childhood |
| 51 | 3.23 | 2.46 | 54 | 42 | 0.0 | 5.2 | Diet, liver and iron | Gangrene of lung; death |
| 52 | 1.8 | 2.5 | 34 | 42 | 5.8 | 13.6 | Diet, liver extract and iron | Typhus; death |

other similar cases have been studied. The anemias resulting from faulty diets are summarized in table 3. In this group, the evidence that supported the conclusion that the anemia resulted from malnutrition was the history of inadequate diets, the presence of undernutrition, the association of nutritional defects such as avitaminosis and edema, and the recovery from the anemia following adequate diets supplemented with substances that tend to build hemoglobin, such as liver and iron.

The importance of faulty diets as a cause of obscure anemias is becoming greater as the various forms are studied. By recognizing this fact and studying these cases, information regarding the exact nature of the substances that are lacking and the deficiency of which is responsible for the development of the anemia may be obtained. In studying

16. Keefer, C. S., and Yang, C. S.: Anemia of Undernutrition: Report of Cases with Results of Treatment, Nat. M. J., China **15**:701, 1929.

the blood of a number of patients with deficiencies due to a lack of vitamins A, B, C and D, we concluded that all of these avitaminoses could exist in man without anemia, although anemia was present in some instances. In the cases in which anemia was present, we concluded it was probably the result of deficiencies in other food substances or of infection. Recently, Mettier, Minot and Townsend[17] reported eight cases of scurvy in which there was a concomitant anemia. They showed that when the patients were given food containing a large amount of vitamin C there was definite improvement in the blood picture with an increase in the reticulocytes. They concluded that the anemia in these patients was due to a lack of vitamin C, but that it was influenced by other factors such as infection, arteriosclerosis or hemorrhage.

TABLE 4.—*Erythrocytes and Hemoglobin in Patients with Edema Resulting from Malnutrition*

| Case | Red Blood Cells, Millions | Hemoglobin (Sahli), per Cent | Comment |
|---|---|---|---|
| 1 | 4.8 | 95 | |
| 2 | 4.6 | 95 | |
| 3 | 7.2 | 134 | Dysentery; dehydration |
| 4 | 4.9 | 85 | |
| 5 | 4.2 | 84 | |
| 6 | 4.4 | 78 | |
| 7 | 3.04 | 77 | |
| 8 | 3.6 | 75 | |
| 9 | 3.8 | 70 | |
| 10 | 3.4 | 60 | |
| 11 | 3.4 | 60 | |
| 12 | 4.9 | 52 | |
| 13 | 3.0 | 50 | |
| 14 | 4.6 | 49 | |
| 15 | 3.5 | 36 | |
| 16 | 2.1 | 35 | Pneumonia; empyema |

At the time we recorded the observations on the blood in the various avitaminoses, observations on the blood in so-called edema were not given. Since then, sixteen patients with this disorder have been observed and the blood counts of this group are recorded in table 4. From the table it is evident that this condition may be present without anemia. The hemoglobin content, however, was below 80 per cent in eleven patients and below 70 per cent in seven. In the patients with anemia, recovery followed a balanced diet containing adequate amounts of protein, fat and carbohydrate, or it occurred after the use of iron. During recovery, the reticulocytes usually increased as in the other forms of anemia.

It is apparent, then, that anemia develops in many patients who have been on faulty diets, but it is not clear which elements through their deficiency are responsible for the anemia. In spite of this fact, the

17. Mettier, S. R.; Minot, G. R., and Townsend, W. C.: Scurvy in Adults, Especially the Effect of Food Rich in Vitamin C on Blood Formation, J. A. M. A. **95**:1089 (Oct. 11) 1930.

regeneration of the hemoglobin may be accelerated in these cases by adequate diets—liver or iron.

Chart 2 shows the course of the blood in a patient with anemia due to malnutrition.

*Anemias Associated with Chronic Dysentery.*—Anemia associated with chronic dysentery was observed in twenty patients. We[18] have described in detail elsewhere the clinical features and the response of

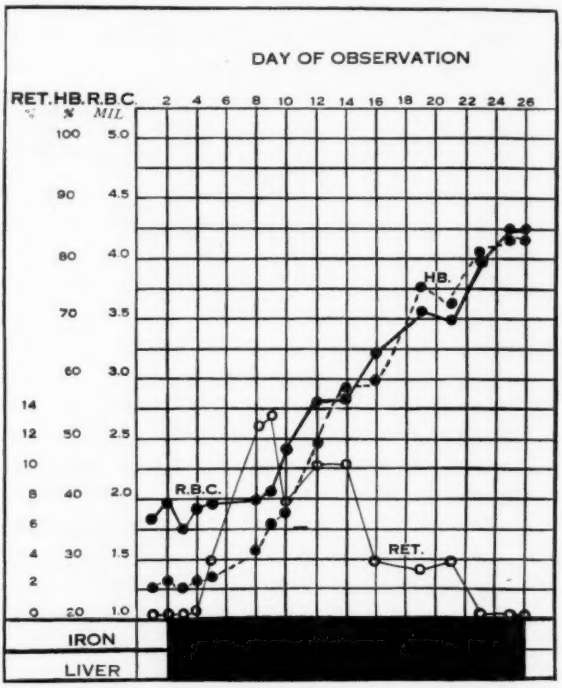


Chart 2.—Chart of patient with anemia resulting from partial starvation. Recovery was rapid following an adequate diet supplemented with liver and iron.

the anemia to treatment in some of these patients. To recapitulate: Anemia usually developed in these patients only after the dysentery had been present for two months or longer, and then it appeared most fre-

18. Keefer, C. S.; Huang, K. K., and Yang, C. S.: The Importance of Undernutrition in the Production of Anemia Associated with Chronic Dysentery and Tuberculosis of the Intestine, Nat. M. J., China **15**:743, 1929. Keefer, C. S.; Yang, C. S., and Huang, K. K.: Anemia Associated with Chronic Dysentery: Clinical Considerations with Special Reference to the Cause and Treatment, Arch. Int. Med. **47**:436 (March) 1931.

quently in those who had been on inadequate diets. The loss of blood in the stools and the part played by the infection and by gastric anacidity, when it was present, were only minor contributory factors. As a result of our observations, we concluded that the anemia resulted from the disturbance in nutrition which followed the chronic diarrhea and from the inadequate diet, and that other factors such as loss of blood, gastric anacidity and infection played an insignificant part.

The anemia varied in its morphologic characteristics and in its severity. Both hyperchromic and hypochromic types of anemia were observed, and the red blood cells were, by actual measurement, smaller or larger than normal. During recovery the reticulocytes increased in number, regardless of the form of treatment. The lower the red cell count before recovery, the higher were the reticulocytes at the peak of the rise.

In the group as a whole, we observed all of the clinical features that are said to be characteristic of pernicious anemia, including atrophy of the papillae of the tongue, subacute combined degeneration, gastric anacidity of the temporary and permanent type and an anemia that responded to liver extract.

The response to treatment varied considerably in different patients. In some, excellent responses were observed following the exhibition of liver extract or iron. In others, varying rates of recovery were observed following other forms of treatment such as high caloric diets or the recovery from the dysentery.

The best methods of treatment in this form of anemia were rest in bed, high caloric diet, local treatment of the intestinal lesions and supplementing the diet with liver and iron. In some cases transfusion of blood was helpful. One cannot predict which form of therapy will be effective in an individual case. If liver fails, it is necessary to give iron in order to determine its potency. The results of treatment are summarized in table 5.

From these observations it is clear that the syndrome of pernicious anemia can appear without changes in gastric acidity in patients who have been on inadequate diets and who have a pathologic process interfering with normal nutrition. Furthermore, these observations support the hypothesis that pernicious anemia is a deficiency disease.

*Anemia Associated with Kala-Azar.*—Kala-azar is a parasitic disease, invariably associated with changes in the blood if the infection has been present for any length of time. In studying a number of patients with kala-azar, Keefer, Khaw and Yang [19] pointed out that there was a depression of all the elements in the blood including the erythrocytes, hemoglobin, white cells and platelets. The leukocytes and platelets were

19. Keefer, C. S.; Khaw, O. K., and Yang, C. S.: The Anemia of Kala-Azar, Nat. M. J., China **15**:731, 1929.

usually reduced before the hemoglobin and erythrocytes. These changes caused symptoms of anemia, predisposition to infection and thrombocytopenic purpura hemorrhagica. In studying the blood platelets in these patients, Yang and Ch'en [20] found that they might be further depressed by treatment with antimony compounds or by some infections.

The cause of the anemia in this disease is not clear, although it is recognized that the characteristic changes in the tissue resulting from the infection are most prominent in the organs that form blood. In many respects these anemias resemble those observed in the so-called myelophthisic anemias, the result of carcinomatoses of the bone marrow,

TABLE 5.—*Results of Treatment in Cases of Anemia Associated with Chronic Dysentery*

| | Red Blood Cells, Millions | | Hemoglobin, per Cent | | Reticulocytes per Cent | | |
|---|---|---|---|---|---|---|---|
| Case | Before Treatment | After Treatment | Before Treatment | After Treatment | Before Treatment | After Treatment | Treatment |
| 16 | 2.9 | 4.3 | 74 | 85 | 4.5 | ... | Spontaneous |
| 17 | 2.2 | 4.5 | 60 | 80 | 2.0 | ... | Spontaneous |
| 18 | 1.0 | 3.75 | 20 | 75 | 0.0 | 1.4 | Transfusion |
| 19 | 3.0 | 4.5 | 50 | 70 | 0.0 | 8.0 | Transfusion |
| 20 | 2.25 | 3.25 | 45 | 60 | 0.0 | 2.0 | Transfusion |
| 21 | 1.44 | 5.21 | 22 | 88 | 1.3 | 28.0 | Full diet; cod liver oil |
| 22 | 1.1 | 4.17 | 21 | 78 | 1.5 | 19.0 | Full diet; cod liver oil |
| 23 | 1.61 | 3.86 | 19 | 70 | 9.0 | 5.0 | Diet; transfusion; iron |
| 24 | 1.10 | 4.62 | 12 | 90 | 0.0 | 26.6 | Iron |
| 25 | 2.8 | 4.7 | 51 | 89 | 3.0 | 8.6 | Iron |
| 26 | 3.59 | 4.36 | 66 | 95 | 1.0 | 9.0 | Iron |
| 27 | 0.66 | 4.53 | 15 | 96 | 1.8 | 38.6 | Liver extract |
| 28 | 2.52 | 3.97 | 54 | 75 | 0.4 | 5.0 | Liver ash; iron; transfusion |
| 29 | 3.05 | 4.89 | 52 | 100 | 0.6 | 6.0 | Liver extract; iron |
| 30 | 2.0 | 5.22 | 35 | 82 | 0.8 | 5.6 | Liver extract; liver and iron |
| 31 | 2.35 | 3.58 | 54 | 85 | 1.2 | 7.6 | Liver extract; liver and iron |
| 32 | 4.46 | 5.0 | 52 | 80 | 0.0 | 14.4 | Liver extract; liver and iron |
| 33 | 1.30 | 1.20 | 34 | 35 | 1.4 | 1.8 | Liver extract |
| 34 | 1.47 | 2.62 | 31 | 56 | 1.2 | 5.4 | Transfusion; diet |
| 35 | 3.05 | 2.80 | 45 | 46 | 1.6 | 2.8 | Iron |

osteosclerosis or leukemia. The exact method of inhibition of the formation of blood in these cases, however, remains a mystery.

In treating these patients for anemia, we found that several measures were useful; namely, transfusion of blood, treatment of the infection with antimony compounds, elimination of intercurrent infections and improving the general nutritional state. The results are summarized in table 6.

*Anemias of Pregnancy.*—The so-called anemias of pregnancy are seen most frequently during the latter term of gestation and occur more often in women who have had multiple pregnancies, particularly when the pregnancies have occurred in rapid succession. The anemia may recur in subsequent pregnancies, and many cases show a tendency to spontaneous recovery following childbirth. The severity of the anemia

20. Yang, C. S., and Ch'en, K. T.: The Blood Platelets in Kala-Azar, Nat. M. J., China **16**:34, 1930.

varies and is characterized by a depression of the erythrocytes and the hemoglobin. Pallor and the symptoms of anemia are present; and in some cases, fever, retinal hemorrhages, moderate cardiac enlargement with hemic murmurs, enlargement of the liver and spleen and edema of the lower extremities may be observed. The leukocyte count is usually normal.

The treatment for these anemias has changed during the past few years, since it has been shown that regeneration of the hemoglobin and the red cells can be accelerated by the feeding of liver or liver

TABLE 6.—*Anemia Associated with Kala-Azar*

| Case | Red Blood Cells, Millions | | Hemoglobin, per Cent | | Reticulocytes, per Cent | | Type of Treatment |
|---|---|---|---|---|---|---|---|
| | Before Treatment | After Treatment | Before Treatment | After Treatment | Before Treatment | After Treatment | |
| 69 | 2.25 | 3.0 | 36 | 45 | ... | ... | Urea stibamine |
| 70 | 2.56 | 4.0 | 45 | 65 | ... | ... | Urea stibamine |
| 71 | 3.00 | 3.5 | 55 | 66 | ... | ... | Urea stibamine |
| 72 | 2.5 | 4.0 | 55 | 85 | ... | ... | Urea stibamine |
| 73 | 3.5 | 4.0 | 65 | 70 | ... | ... | Urea stibamine |
| 74 | 3.25 | 4.0 | 60 | 55 | ... | ... | Urea stibamine |
| 75 | 2.25 | 3.5 | 42 | 70 | ... | ... | Urea stibamine |
| 76 | 2.5 | 3.0 | 45 | 45 | ... | ... | Urea stibamine |
| 77 | 1.5 | 3.25 | 25 | 50 | ... | ... | Urea stibamine |
| 78 | 3.0 | 4.25 | 55 | 80 | ... | ... | Urea stibamine |
| 79 | 3.0 | 4.0 | 50 | 80 | ... | ... | Urea stibamine |
| 80 | 3.5 | 4.25 | 65 | 70 | ... | ... | Urea stibamine |
| 81 | 4.0 | 4.0 | 60 | 60 | ... | ... | Urea stibamine |
| 82 | 4.0 | 4.70 | 70 | 85 | ... | ... | Urea stibamine; transfusion |
| 83 | 1.5 | 2.5 | 28 | 40 | 2.1 | 2.1 | Urea stibamine; transfusion |
| 84 | 1.5 | 1.7 | 18 | 45 | 4.1 | 3.1 | Urea stibamine; transfusion |
| 85 | 2.0 | 4.0 | 40 | 60 | 3.1 | 3.0 | Urea stibamine; transfusion |
| 86 | 3.5 | 4.5 | 60 | 90 | 2.1 | 2.0 | Urea stibamine; transfusion |
| 87 | 1.5 | 2.5 | 15 | 30 | 0.0 | 1.0 | Urea stibamine; transfusion |
| 88 | 2.5 | 3.75 | 40 | 55 | 2.0 | 2.0 | Urea stibamine; transfusion |
| 89 | 1.8 | 4.25 | 35 | 80 | 2.0 | 2.0 | Urea stibamine; liver and iron |
| 90 | 2.25 | 2.25 | 45 | 35 | 2.0 | 2.4 | Urea stibamine; liver and iron |
| 91 | 3.0 | 4.5 | 40 | 70 | 2.0 | 2.0 | Urea stibamine; liver and iron |
| 92 | 2.4 | 2.0 | 40 | 70 | 2.0 | 2.0 | Urea stibamine; liver and iron |
| 93 | 2.1 | 4.0 | 44 | 45 | 0.4 | 4.6 | Urea stibamine; liver and iron |
| 94 | 2.1 | 4.0 | 35 | 75 | 2.0 | 8.0 | Urea stibamine; liver and iron |
| 95 | 2.5 | 4.0 | 47 | 67 | 2.0 | 10.0 | Urea stibamine; liver and iron |
| 96 | 3.76 | 4.0 | 60 | 70 | 1.6 | 3.2 | Urea stibamine; liver and iron |

extract, or by combinations of liver and iron, or by iron alone. This form of treatment has been reviewed recently by Vaughan,[13] Strauss [21] and Yang and Keefer.[22] We have had an opportunity of observing nine cases, and in our experience the feeding of liver and iron has been of value. These cases are summarized in table 7. Infection may inhibit the rate of regeneration of the blood, but many immature cells may appear in the peripheral circulation following treatment with liver even under these circumstances. In one such patient whom we observed, the bone marrow showed a marked erythroblastic hyperplasia.

21. Strauss, M.: Chlorotic Anemia of Pregnancy: A Report of Three Cases, Am. J. M. Sc. **180**:818, 1930.

22. Yang, C. S., and Keefer, C. S.: The Anemias of Pregnancy, Nat. M. J., China **16**:159, 1930.

The cause of these anemias remains obscure. Certain facts exist, however, which suggest that these anemias develop in the patients who do not receive enough of the essential materials necessary for the regeneration of the hemoglobin during pregnancy, and the increased demands caused by the pregnancy are sufficient to cause the anemia to appear. These cases should be investigated further with these facts in mind.

*Anemia Associated with Infestation Due to Hookworm.*—The cause of the anemia in infestation due to hookworm is unknown. We have studied seven patients with moderately severe anemia and infestation

TABLE 7.—*Anemia Associated with Pregnancy*

| Case | Red Blood Cells, Millions | | Hemoglobin, per Cent | | Reticulocytes, per Cent | | Comment |
|---|---|---|---|---|---|---|---|
| | Before Treatment | After Treatment | Before Treatment | After Treatment | Before Treatment | After Treatment | |
| 53 | 1.0 | 3.75 | 25 | 78 | ... | ... | Blood transfusions (three) |
| 54 | 2.0 | 4.25 | 20 | 75 | 1.0 | 2.5 | Blood transfusions (three) |
| 55 | 2.5 | 4.0 | 45 | 80 | 1.0 | 2.0 | Blood transfusions and typhoid |
| 56 | 4.15 | 5.0 | 54 | 85 | 2.2 | 7.0 | Iron |
| 57 | 2.15 | 3.75 | 36 | 75 | 0.0 | 11.0 | Liver |
| 58 | 2.97 | 4.32 | 53 | 81 | 0.8 | 7.0 | Liver and iron |
| 59 | 3.01 | 4.83 | 43 | 64 | 2.6 | 3.6 | Liver* |
| 60 | 2.0 | 3.0 | 40 | 61 | 0.2 | 11.0 | Iron; liver extract* |
| 61 | 1.37 | 2.89 | 22 | 47 | 0.2 | 13.0 | Liver and iron; pyelonephritis; death |

* Under hospital observation only two weeks. Blood counts normal six months after discharge.

TABLE 8.—*Results of Treatment for Anemia Associated with Infestation Due to Hookworm*

| Case | Red Blood Cells, Millions | | Hemoglobin, per Cent | | Reticulocytes, per Cent | | Type of Treatment | Comment |
|---|---|---|---|---|---|---|---|---|
| | Before Treatment | After Treatment | Before Treatment | After Treatment | Before Treatment | After Treatment | | |
| 62 | 3.36 | 5.11 | 40 | 91 | 1.8 | 14.0 | Liver and iron | 128 worms |
| 63 | 2.38 | 4.6 | 30 | 85 | 5.0 | 13.0 | Liver and iron | ? |
| 64 | 3.5 | 4.89 | 40 | 86 | 3.6 | 10.0 | Liver and iron | ? |
| 65 | 2.55 | 4.43 | 47 | 86 | 4.2 | 8.0 | Liver and iron | 10 worms |
| 66 | 2.94 | 5.0 | 32 | 90 | 1.4 | 8.0 | Liver and iron | 51 worms |
| 67 | 2.31 | 4.24 | 36 | 100 | 1.4 | 9.8 | Iron | 72 worms |
| 68 | 2.5 | 5.0 | 45 | 96 | 1.0 | 12.0 | Iron | 146 worms |

caused by hookworm and have found that they may recover from the anemia following the administration of liver and iron while they continue to carry the worms. These cases are summarized in table 8.

All of the patients whom we studied had only mild infestations, so that the question may be raised whether the parasitic disease had anything to do with the presence of anemia. At the present time all that can be said is that the patients had anemia associated with infestation due to hookworm and that no other cause was obvious, except that most of the patients had been on faulty diets prior to admission. It will be of considerable interest to determine whether or not the faulty

diets which are consumed by many patients with infestation produced by hookworm are not a predisposing factor in producing anemia and also whether adequate diets may not be capable of accelerating regeneration of the blood before as well as after the expulsion of the worms.

It has been pointed out previously that recovery from the anemia may be slow following the expulsion of the worms and that it can be accelerated by giving iron.[23] Day and Ferguson [24] never observed complete recovery following this form of treatment until after treatment of the infestation. Whether the complete recoveries that we observed after the administration of liver and iron in infested patients can be obtained in similar patients with a heavy burden of worms remains unsettled. It is clear, however, that recovery from the anemia in this condition can be accelerated by giving an adequate diet supplemented with iron.

Schapiro [25] recently called attention to the discrepancy existing between the worm burden and anemia resulting from infestation with hookworms, and expressed the opinion that faulty nutrition is the factor that controls anemia in many of these patients. It remains to be proved, therefore, whether infestation due to hookworm is in itself capable of producing anemia.

*Anemia Associated with Miscellaneous Conditions.*—The cases included in this group are summarized in table 9. A few of them may be discussed in detail.

Malaria: The anemia resulting from malarial infection may be extreme and is usually due to a destruction of red blood cells. In most instances there is an increase in the reticulocytes, and Yang and Berglund [26] discussed the relationship between a hemolytic process and the response of the reticulocytes in this and other forms of anemia due to excessive destruction of blood. Some observers, notably Seyfarth,[27] called attention to the diagnostic significance of an increased reticulocyte count in the anemia due to malaria. We have studied three patients with

23. Dock, G., and Bass, C. C.: Hookworm Disease, St. Louis, C. V. Mosby Company, 1910. Keefer, C. S., and Yang, C. S.: The Value of Liver and Iron in the Treatment of Secondary Anemia, J. A. M. A. **93**:575 (Aug. 24) 1929. Kobayashi, Toshiyo: Sur les phénomènes régénératifs des hématies dans les anémies de l'ankylostomiase, Sang **2**:129, 1929.

24. Day, H. B., and Ferguson, A. R.: The Treatment of Ankylostoma Anaemia, Lancet **2**:82, 1914.

25. Schapiro, L.: Hookworm Infestation in an Indian (Guaimi) and Non-Indian Population of Panama, Am. J. Trop. Med. **10**:365, 1930.

26. Yang, C. S., and Berglund, H.: Differences in Reticulocyte Behavior in Anemia from Malaria and in Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **26**:417 (March) 1929.

27. Seyfarth, C.: Experimentelle und klinische Untersuchungen über die vitalfärbbaren Erythrozyten, Folia haemat. **34**:7, 1927.

severe anemia due to malaria, and in each case there was an increase in the reticulocytes before treatment with quinine was given, and recovery occurred promptly following the cure of the malaria. There are cases, however, in which the period of recovery may be slow, but in these the malarial infection is usually complicated by infestation due to hookworm and by malnutrition.[28]

TABLE 9.—*Anemia Associated with Miscellaneous Conditions*

| Case | Diagnosis | Red Blood Cells, Millions | | Hemoglobin, per Cent | | Reticulocytes, per Cent | | Treatment |
|---|---|---|---|---|---|---|---|---|
| | | Before Treatment | After Treatment | Before Treatment | After Treatment | Before Treatment | After Treatment | |
| 97 | Malaria | 0.88 | 4.13 | 25 | 82 | 23.0 | ... | Quinine |
| 98 | Malaria | 2.0 | 4.5 | 40 | 85 | 11.5 | ... | Quinine |
| 99 | Malaria | 2.7 | 4.43 | 50 | 80 | 7.2 | 8.0 | Quinine |
| 100 | Chlorosis | 4.0 | 5.0 | 55 | 85 | 0.0 | 7.0 | Iron |
| 101 | Chlorosis | 3.8 | 4.0 | 35 | 65 | 0.0 | 2.0 | Iron |
| 102 | Chlorosis | 4.75 | 5.25 | 50 | 75 | 0.0 | 2.0 | Iron |
| 103 | Chlorosis | 5.0 | 5.0 | 50 | 85 | 0.0 | 6.0 | Iron and liver |
| 104 | Anemia five years after splenectomy | 3.76 | 5.47 | 33 | 86 | 0.0 | 8.0 | Iron |
| 105 | Anemia following splenectomy | 2.5 | 5.0 | 50 | 80 | 0.0 | 8.0 | Iron |
| 106 | Splenic anemia | 3.52 | 3.78 | 52 | 51 | 1.0 | 5.8 | Liver |
| 107 | Splenic anemia | 2.25 | 3.4 | 50 | 65 | 8.0 | 8.0 | Iron |
| 108 | Anemia following splenectomy | 3.5 | 4.1 | 52 | 60 | 0.0 | 5.0 | Spontaneous |
| 109 | Splenic anemia | 3.5 | 4.0 | 50 | 60 | 0.0 | 5.0 | Spontaneous |
| 110 | Chronic nephritis | 2.27 | 2.9 | 43 | 58 | 0.0 | 3.0 | Cod liver oil diet* |
| 111 | Tuberculosis of intestines; keratomalacia | 1.39 | 1.70 | 29 | 38 | 3.3 | 14.4 | Liver extract; cod liver oil; iron |
| 112 | Tuberculosis of intestines | 3.08 | 4.22 | 58 | 81 | 0.6 | 2.2 | Liver and iron; transfusion |
| 113 | Tuberculosis of intestines | 3.33 | 3.24 | 52 | 48 | 0.0 | 3.6 | Liver and iron |
| 114 | Tuberculosis of intestines | 2.76 | 3.33 | 43 | 52 | 0.6 | 4.0 | Liver and iron |
| 115 | Aplastic anemia | 1.28 | 1.95 | 28 | 42 | 0.4 | 2.4 | Liver and iron |
| 116 | Aplastic anemia | 1.24 | 1.20 | 31 | 30 | 0.2 | 3.8 | Liver and iron |
| 117 | Pernicious anemia | 2.02 | 3.94 | 50 | 82 | 0.0 | 5.0 | Liver extract |
| 118 | Pernicious anemia | 1.5 | 4.0 | 35 | 80 | 0.0 | 15.0 | Liver extract |
| 119 | Syphilis | 2.23 | 3.32 | 30 | 49 | 4.0 | 4.0 | Iron |
| 120 | Pellagra; syphilis | 3.09 | 3.5 | 58 | 68 | 1.0 | 3.6 | Iron |
| 121 | Syphilis | 3.89 | 3.8 | 52 | 66 | 0.0 | 20.0 | Iron* |
| 122 | Typhoid fever | 3.19 | 4.52 | 58 | 86 | 3.4 | 9.2 | Liver and iron |
| 123 | Cirrhosis of liver | 3.36 | 3.59 | 45 | 60 | 1.2 | 1.8 | Liver |
| 124 | Acute leukemia | 1.18 | 1.23 | 29 | 29 | 0.4 | 5.8 | Liver and iron |
| 125 | Purpura hemorrhagica | 3.3 | 5.2 | 63 | 90 | 1.8 | 8.1 | Transfusion |
| 126 | Cancer of stomach | 2.5 | 2.25 | 50 | 52 | 2.0 | 2.2 | Liver extract |

* The patient died.

Chlorosis: There were four female patients with a chlorotic type of anemia who recovered promptly following the exhibition of iron. The cause of these anemias was unknown, but we felt that relative starvation with respect to iron over a long period of time was probably responsible for them. Two of the patients had gastric anacidity. It is well to remember that there is a small but definite group of cases of the

28. Darling, S. T.; Barker, M. A., and Hacker, H. P.: Hookworm and Malaria Research in Malaya, Java and Fiji Islands: Report of Uncinariasis Commission to Orient, 1915-1917, New York, Rockefeller Foundation, International Health Board, 1920, publication 9.

simple type of anemia resembling the so-called chlorosis which occurs in both sexes, is associated with gastric anacidity, occurs at all ages, has a tendency to recur, and is improved by giving large doses of iron. Such cases have been adequately described by Faber and Gram.[29] Mettier and Minot[30] also described cases of chlorotic anemia associated with disturbances in gastric secretion responding to iron therapy. In many of these patients the dietary habits are of importance. Some of them show an increase in reticulocytes during recovery, and we have noticed that this response is more marked if there is an increase of the total red cell count as well as of the hemoglobin.

Splenic Anemia: One patient, who had had a splenectomy five years before coming under observation a second time, was observed with a chlorotic type of anemia which improved following the administration of iron (case 103). The spleen had been removed on account of splenomegalia with leukopenia and anemia. This patient had remained well until shortly before the second admission to the hospital. At the time of her readmission, gastric anacidity was present and disappeared following recovery from the anemia.

This observation was of interest to us in view of some of the cases of so-called splenic anemia reported by Hanrahan.[31] He pointed out that splenectomy was only of temporary therapeutic value in many patients with this syndrome, and that anemia recurred in a number.

There were two other patients who had had a splenectomy for splenic anemia and showed no improvement of the anemia following this procedure. Three other patients with a similar syndrome were given liver or iron. No improvement followed the feeding of liver in one, and only slight improvement followed the use of iron in the other two.

Tuberculosis of the Intestines: In a previous communication by Keefer, Huang and Yang[32] it was pointed out that the patients with intestinal tuberculosis of the ulcerative type and anemia were those who had diarrhea or constipation alternating with diarrhea. It was concluded that the process interfering with nutrition, together with the disturbances in appetite, probably accounted for the anemia. When similar patients were given liver and iron, no improvement of the anemia occurred. The improvement in case 112 was due to a transfusion of blood.

In our experience, no improvement of the anemia was observed when liver and iron were exhibited to patients with aplastic anemia, acute

29. Faber, K., and Gram, H. C.: Relations Between Gastric Achylia and Simple and Pernicious Anemia, Arch. Int. Med. **34**:658 (Nov.) 1924.

30. Mettier, S. R., and Minot, G. R.: The Effect of Iron in Blood Formation as Influenced by Changing the Acidity of the Gastric Contents in Certain Cases of Anemia, J. Clin. Investigation **7**:510, 1929.

31. Hanrahan, E. M.: Splenic Anemia: A Study of End-Results with and without Splenectomy, Arch. Surg. **10**:639 (March) 1925.

32. Keefer, Huang and Yang (footnote 18, first reference).

leukemia, cirrhosis of the liver, anemia associated with syphilitic infection or chronic nephritis.

The patient who developed anemia following typhoid fever without hemorrhage was interesting in that he was unable to take large amounts of food during the course of his illness because of vomiting and the presence of a persistent diarrhea associated with an amebic dysenteric infection. As a result anemia and edema developed late in the course of the disease, and the patient recovered from both conditions when he was able to take an adequate diet.

Nothing has been added to our knowledge of the anemia of typhoid fever since Thayer's [33] complete review of the subject a number of years ago. Its cause is obscure although Longcope [34] described changes of an aplastic nature in the bone marrow of these patients. When one studies the cases of patients with typhoid fever who have been treated by the administration of large amounts of food instead of by the method of starvation during the course of the disease, anemia without intestinal hemorrhage is infrequently observed.[35] Many of the complications described in the older literature as occurring during typhoid fever, such as anemia, polyneuritis, transitory ascites and the various ocular complications, should be reviewed in the light of our present knowledge regarding the influence of malnutrition in producing such changes in the tissues.

## RESULTS OF TREATMENT

The results obtained with various forms of treatment are summarized in chart 3. It is clear that conspicuous increases in the regeneration of the hemoglobin were obtained in many cases with various forms of therapy, and it is also evident that no demonstrable effect was obtained in other cases following the same form of treatment. The most striking results were seen after the administration of iron or of liver supplemented with iron. From the chart it appears that the results obtained following the administration of iron were as noticeable as those following the administration of liver and iron. In some cases this was true. However, when individual cases were studied it could be shown without doubt that the regeneration of the hemoglobin was greater in some cases following the exhibition of liver and iron than when either was given alone. This is illustrated in chart 4. It is obvious from these cases that if the regeneration of hemoglobin were occurring following the use of liver

33. Thayer, W. S.: Two Cases of Post-Typhoid Anemia, Johns Hopkins Hosp. Rep. **4**:83, 1894; Observations on the Blood in Typhoid Fever, Bull. Johns Hopkins Hosp. **8**:47, 1899.

34. Longcope, W. T.: The Bone Marrow in Typhoid Fever, Bull. Ayer Clin. Lab., Pennsylvania Hosp. **2**:1, 1905.

35. Zia, S. H.: Typhoid Fever: A Clinical Study of 256 Cases in Peking, Nat. M. J., China **14**:105, 1928.

or iron, the rate of increase could be accelerated by adding the other substance. On the other hand, in some cases, when no response was demonstrable following the use of liver, the addition of iron was followed by improvement.

It is clear, therefore, that the maximum effect may be obtained in some cases following the administration of liver and iron, whereas in others, it follows the administration of iron or liver alone.

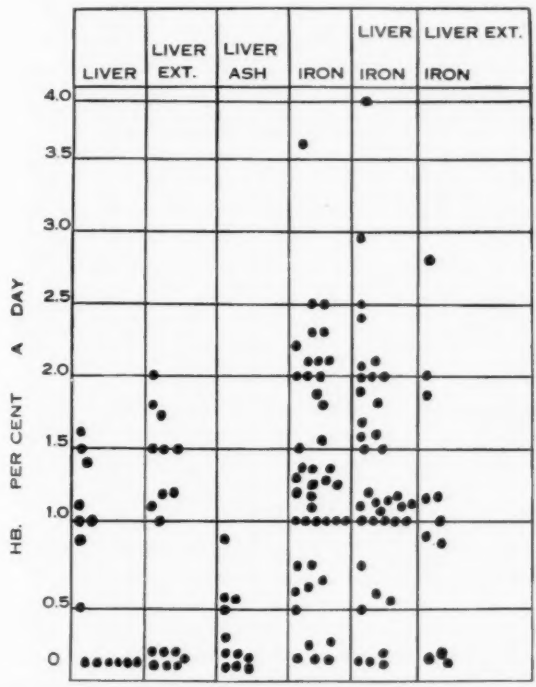


Chart 3.—The rate of regeneration of the hemoglobin following various forms of treatment. From this chart it appears that iron may produce as good results as liver and iron. This is not true in all cases (see chart 4).

The results obtained with various forms of treatment we have studied may be discussed in greater detail.

*The Value of Liver.*—We [36] have found liver to be of value in the treatment for posthemorrhagic anemia, anemia resulting from faulty

36. Keefer, C. S., and Yang, C. S.: The Value of Liver and Iron in the Treatment of Secondary Anemia, J. A. M. A. **93**:575 (Aug. 24) 1929. Yang, C. S., and Keefer, C. S.: Liver and Iron in the Treatment of Secondary Anemia, Nat. M. J., China **15**:721, 1929.

diets and in some of the anemias associated with pregnancy, infestation due to hookworm and with dysentery. We have not been able to demonstrate that it is potent in increasing the regeneration of hemoglobin in patients with anemia associated with tuberculosis of the intestines and diarrhea, nor in aplastic anemia, the anemia of kala-azar and other anemias when complicated by intercurrent infections. The daily rate of

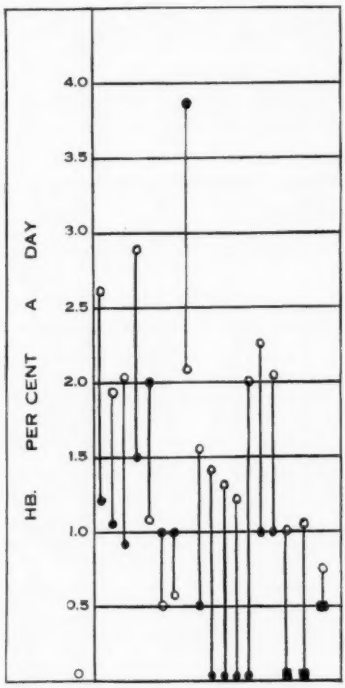


Chart 4.—This chart illustrates the regeneration of the hemoglobin in patients (each line represents an individual patient) who received liver and then liver and iron. The solid dots represent the response to liver and the circles the results when iron was added. In some cases iron was given before liver was added. The squares indicate the response following the administration of liver extract. It is apparent that in some cases combinations of liver and iron are more effective than either one alone.

the regeneration of hemoglobin that we have observed following liver therapy in all forms of anemia is summarized in chart 3.

The results of feeding liver in the various anemias are in agreement with the observations of other observers, and the question has been subjected to a critical review by Vaughan.[13] She pointed out that

treatment with liver was most effective in pernicious anemia, and in some of the anemias associated with pregnancy and so-called sprue. She also stated that it was potent in posthemorrhagic anemia and some of the obscure nutritional anemias. From her observations and the review of the reported cases, she concluded that liver was probably most effective in the anemias associated with a hyperplastic bone marrow, but the reason for its ineffectiveness in other cases was not clear. It is evident, therefore, that liver is of value in the treatment for some forms of anemia, but it cannot be denied that it is of no demonstrable value in the treatment for others. This is the experience of all observers. These failures have been attributed to various factors, such as the presence of infection, the feeding of insufficient quantities of liver, or giving it over too short a period of time, or to a difference in the fundamental disturbance that exists in the different anemias. There is considerable evidence that all of these factors are of importance in explaining many of the failures observed. To give better correlation, we shall review this evidence briefly.

It will be admitted generally that many infections cause increased destruction of blood cells and also inhibit the formation of blood. The explanation for this phenomenon is not clear. There are certain infections, however, in which an anemia may be improved following the use of liver or liver extract, in spite of the persistence of infection. We observed such responses in some patients with anemia associated with chronic dysentery, so that infection may be only one factor in explaining the inhibition of the formation of red cells when it is associated with an anemia. We demonstrated that other factors such as deficient diets are of importance in many such cases.

Besides the inhibitory effect of infection on the formation of blood following the administration of liver, it has been stated that the failure to observe positive responses is due to the feeding of inadequate amounts of liver over too short a period of time. At the present time, the amount of liver that is necessary for the maximum output of hemoglobin in the forms of anemia in which it is effective is unknown. It is to be noted, however, that at least 300 or 400 Gm. must be given daily and for a period of at least two weeks before a failure can be recorded. While it is undoubtedly true that inadequate doses of liver may account for many of the observed failures, it is not the case in all, because we have observed negative responses to liver therapy when the dose has been large, but positive responses in the same patients when iron was given. While it would appear that infection and inadequate dosage of liver are responsible for some of the failures observed, there remain other factors which are incompletely understood.

The most likely explanation for this varying response is the difference in the fundamental disturbance existing in different anemias. It is now

evident from the experimental work of Whipple and Robscheit-Robbins, and others, that there are a number of factors which influence the regeneration of the blood, and a disturbance of one or more of these factors will result in anemia. These observations are being confirmed in the anemias in man as information accumulates. In discussing the fundamental differences existing in some of the anemias, such as pernicious anemia, which responds in a spectacular way to the feeding of liver, and other forms of anemia which do not show such remarkable improvement, Whipple, Robscheit-Robbins and Walden [37] advanced the following points: In pernicious anemia there is a faulty construction or a lack of the constituents that form the stroma of the red cells, and no deficit of the hemoglobic pigments. When liver is fed to these patients, the missing element necessary for the maturation of red cells and the constituents that form stroma of the red cells are supplied, and recovery occurs promptly. In the case of the so-called "secondary" anemias, they postulate that there is a deficit of pigment-producing substances of which there are organic and inorganic elements, and recovery in these anemias will not occur until these substances are supplied in the diet. In other words, they are of the opinion that both pernicious anemia and many of the so-called secondary anemias are due to a deficiency of substances necessary for the formation of red cells and hemoglobin, and recovery will not occur until the necessary substances are supplied. If one accepts the fact that the liver and the kidney supply a maximum amount of substances most suitable for the formation of red cells and hemoglobin, and that both forms of anemia mentioned are due to a deficiency of these substances, it is difficult to understand why spectacular results do not occur in all cases of anemia when liver is fed. The explanation offered by Whipple, Robscheit-Robbins and Walden [37] is that it is difficult for patients with secondary anemias due to lack of pigment-producing substances to take the required amount of liver which produces spectacular results. In other words, it is a matter of quantitative factors, and it would appear that the liver and the kidney contain more stroma-building substances than pigment-building materials.

In the main, we are in agreement with these conclusions and feel that the explanation offered for the difference in response to liver serves as an excellent working hypothesis in the study of the various anemias in man. Certain facts, however, are of importance. First of all, if one excludes the cases in which there are factors inhibiting the effect of liver, such as infection or damage to the bone marrow, there remain other cases which fail to respond to liver but respond to iron. On the other hand, in other patients with secondary forms of anemia the

37. Whipple, G. H.; Robscheit-Robbins, F. S., and Walden, G. B.: Blood Regeneration in Severe Anemia: Liver Fraction Potent in Anemia Due to Hemorrhage, Am. J. M. Sc. **179**:628 (May) 1930.

response to liver may be as spectacular as that observed in pernicious anemia, and improvement may occur rapidly. As a result of these observations, it has been pointed out previously that some of the clinical anemias were probably due to a lack of iron, whereas others were due to a lack of substances found in the liver or the kidney, and in still others both substances were lacking. If these ideas were expressed in the terms used by Whipple and Robscheit-Robbins, it would be stated that in some anemias, the deficiency is due to a lack of stroma-building substances (pernicious anemia); in others to a lack of pigment-building materials, and in others, to a lack of both stroma-building and pigment-building substances.

One of the difficulties in drawing conclusions from any clinical study at the present time lies in our lack of information regarding quantitative factors and in our inability to classify the anemias in man in any way other than by the results obtained following treatment. It is impossible to predict in a given case whether the anemia will respond to liver alone, iron alone, or to a combination of both. Further study is needed before these questions can be settled.

*The Value of Iron.*—It is now generally acknowledged that iron is potent in increasing the regeneration of the hemoglobin in many forms of anemia. The experimental evidence supporting this statement was reviewed recently by Robscheit-Robbins.[38] Whipple and Robscheit-Robbins [39] designated the response obtained by iron and certain other metals such as copper as the "salt effect," and they found that the maximum output of hemoglobin may be observed in dogs after feeding 60 mg. of iron a day and that additional amounts of iron do not cause an increased output of hemoglobin.

The recent studies of Mettier and Minot,[40] and Keefer, Huang and Yang [41] indicated that iron is of value in the treatment for many of the chlorotic types of anemia, posthemorrhagic anemias, some of the anemias due to malnutrition, pregnancy and infestation produced by hookworm. The dose of iron that produces the maximum output of hemoglobin in man, when it is effective, is unknown. We were able to show that a positive effect could be produced in some patients by 90 mg. a day, but at that time we did not have a sufficient number of observations

38. Robscheit-Robbins, F. S.: Regeneration of Hemoglobin and Erythrocytes, Physiol. Rev. **9**:666, 1929.

39. Whipple, G. H., and Robscheit-Robbins, F. S.: Blood Regeneration in Severe Anemia: XVI. Optimum Iron Therapy and Salt Effect, Am. J. Physiol. **92**:362, 1930.

40. Mettier, S. R., and Minot, G. R.: The Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastric Contents in Certain Cases of Anemia, J. Clin. Investigation **7**:510, 1929.

41. Keefer, C. S.; Huang, K. K., and Yang, C. S.: Liver Extract, Liver Ash, and Iron in the Treatment of Anemia, J. Clin. Investigation **9**:533, 1930.

to determine the minimum effective dose of iron in the various anemias. It was clear, however, that the optimum dose of iron varied in different forms of anemia so that if a positive effect is to be obtained large doses must be given.

When a positive effect was obtained following the administration of iron, the reticulocytes usually increased. In most cases, the increase at the peak of the rise was inversely proportional to the total number of red cells present before the beginning of treatment. There were exceptions to this rule, but they were observed usually in patients whose blood showed a low color index.

*The Value of Liver Ash.*—The inorganic constituents of liver, when given in the form of liver ash, have been found to be effective in increasing the regeneration of hemoglobin and red cells in dogs with posthemorrhagic anemia, and in the nutritional anemia of rats. Elden and McCann [42] reported the preliminary phenomenon of a remission when it was exhibited to a patient with pernicious anemia, but complete recovery did not ensue until liver extract (Lilly, no. 343) was given. A small group of ten patients with anemia was studied following feeding with liver ash. It was given in amounts equivalent to 300 Gm. of whole liver a day, and on chemical analysis this amount contained 21 mg. of iron.

The results following the use of liver ash were never striking, but when the same patients were given iron in the form of ferrous carbonate in doses ranging between 90 and 480 mg. a day, a positive effect could be demonstrated by an increase in the reticulocytes and in the rate of the regeneration of the hemoglobin.

The results are summarized in chart 5. It is certain that iron was more efficacious than the liver ash.

The reason for our failure to observe positive effects following the use of liver ash was probably due to the small amount of iron contained in it, since we have shown that positive effects from iron therapy may be obtained in some patients with 90 mg. or more a day.

*The Value of Liver and Iron.*—The results obtained in the regeneration of hemoglobin following the use of liver and iron are plotted in chart 3. It may be observed that the results obtained from the feeding of iron were as striking as those obtained following the administration of liver and iron, and in many cases this was true. However, because many of these patients received liver and iron together from the beginning of the observations it was impossible to separate the effect of the iron from that of the liver, and the results are misleading. In the cases in which the effect of the iron could be separated from that of

42. Elden, C. A., and McCann, W. S.: Effect of Ash of Liver on Blood Regeneration in Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **25**:746 (June) 1928.

the liver, due to the fact that each substance was given alone for a period of time varying from ten to fourteen days, it was shown that the effect of liver could be enhanced by iron. This was illustrated in chart 4. It may be seen that in many cases the results were more striking following both than when either was given alone. In some instances there was no response following the ingestion of liver, but an excellent response following iron.

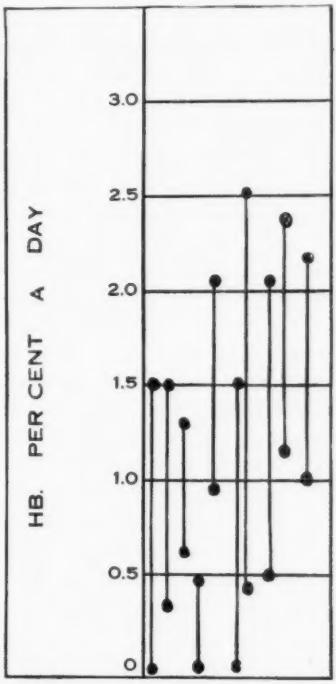


Chart 5.—This chart illustrates the difference in the regeneration of the hemoglobin following treatment with liver ash and iron. The lower dots represent the daily rate of regeneration of the hemoglobin following the administration of liver ash in amounts equal to 300 Gm. of whole liver. This amount contained 21 mg. of iron. The upper dots represent the response following larger doses of iron. The two cases at the extreme right illustrate the difference in regeneration of the hemoglobin following 180 mg. and 480 mg. of iron a day.

It is evident, therefore, that in some anemias, at least, liver and iron given in combination are more effective than when either one is given alone. There are other cases in which the maximum effects may be obtained with iron alone or liver alone.

*Value of Liver Extract and Iron.*—What we have said regarding whole liver and iron also applies to liver extract and iron. That is to say, in some cases, maximum responses may be obtained with liver extract and iron, and in others with iron alone. We have found liver extract potent in some of the nutritional anemias of childhood, in some anemias associated with chronic dysentery, pregnancy and infestation due to hookworm. It has been of little demonstrable value in posthemorrhagic anemia.

### THE RESPONSE OF THE RETICULOCYTES

One of the best methods of determining the activity of the bone marrow and the efficiency of any form of treatment for the various anemias is the study of the response of the reticulocytes. Minot and Murphy [43] first emphasized this method of study in evaluating treatment with liver in pernicious anemia, and later the same method was used in testing the potency of liver extract in the same disease. They found that the height of the increase in reticulocytes depended on the level of the red cell count and the dosage of liver extract. That is to say, the lower the red count before treatment and the larger the dose of liver or liver extract, the higher the reticulocytes increased at the peak of the rise.

In a previous study of fifty-eight cases of secondary anemia, we [44] found that the increase of the reticulocytes varied with the type of treatment, the level of the red blood count before treatment was begun and the cause of the anemia.

The reticulocyte responses observed in the present cases have been tabulated in the tables and summarized in charts 6 and 7. Chart 6 illustrates the highest reticulocyte count observed in all of the cases when plotted against the number of red blood cells before the beginning of therapy. Chart 7 illustrates the highest number of reticulocytes observed in the patients who recovered regardless of the treatment employed. It appears from this chart that the lower the red blood count before the beginning of treatment, the greater the reticulocyte response during recovery. There are, however, a number of exceptions to this statement which require further comment.

In the posthemorrhagic anemias, increases in the reticulocytes were not observed following the ingestion of liver extract, and in some cases the reticulocytes did not increase following transfusions of blood. In

43. Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by a Special Diet, J. A. M. A. **87**:470 (Aug. 14) 1926; A Diet Rich in Liver in the Treatment of Pernicious Anemia, ibid. **89**:759 (Sept. 3) 1927.

44. Yang, C. S., and Keefer, C. S.: The Response of the Reticulocytes in Secondary Anemias Following Various Forms of Treatment, Arch. Int. Med. **45**: 456 (March) 1930.

one case, iron, and in another, liver and iron, caused no increase in spite of recovery. In others, the reticulocytes increased during recovery following the administration of liver and iron, the transfusion of blood, or the use of iron alone.

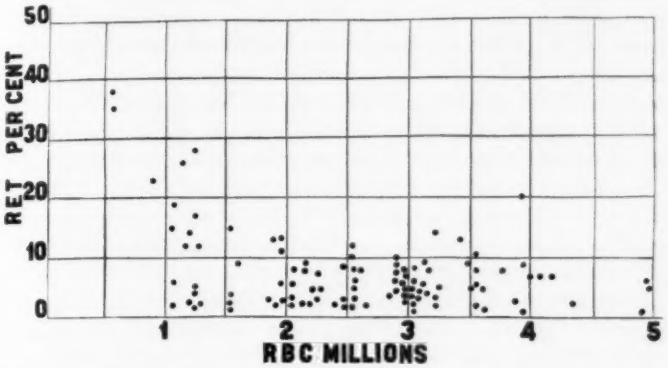


Chart 6.—The reticulocytes at the peak of the rise in all patients regardless of whether or not they recovered.

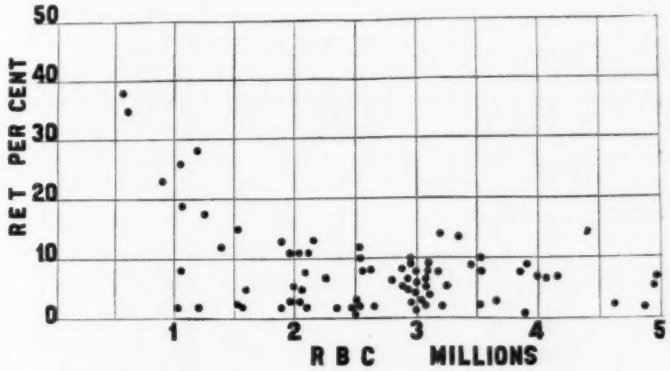


Chart 7.—The reticulocytes at the peak of the rise in the patients who recovered.

In the cases of anemia resulting from chronic dysentery, slight responses were observed in some patients following transfusion, or when the recovery occurred slowly without any special therapy, or when no improvement was observed due to the severity of the infection. In the cases in which prompt recovery from the anemia followed adequate diets or special therapy such as the administration of liver and iron, the reticulocytes were increased.

In the anemias resulting from malnutrition, from infestation due to hookworm and from pregnancy, increases in the reticulocytes were observed regularly except when transfusion of blood was employed, or when the recovery was slow.

In kala-azar, the increase in reticulocytes during recovery was slight except in two patients who had comparatively recent infections. These observations illustrate that when there are pathologic processes in the bone marrow, such as those observed in kala-azar, the reticulocytes may not appear in the circulating blood in greater numbers.

In the cases listed under miscellaneous anemias, increases were noted when recovery occurred, but were usually only slight when no improvement was observed. Occasionally conspicuous increases in the reticulocytes were seen without any improvement in the anemia. In these cases, there was usually a severe infection such as tuberculosis of the intestine which was fatal.

In summary, then, our experience has shown that the reticulocytes may increase during recovery from many forms of anemia, and that the more severe the anemia, the higher the reticulocyte count at the peak of the rise. On the other hand, increases in the reticulocytes may not be observed following transfusion of blood, or in cases in which there is a disorder of the bone marrow such as occurs in kala-azar. In patients with a low color index there may be no increase in the reticulocytes if recovery is slow, and the erythrocyte count remains stationary. If, on the other hand, there is an increase of both the erythrocytes and the hemoglobin during recovery, the reticulocytes may increase. Furthermore, if the reticulocytes have increased to a maximum before treatment is begun, a further rise may not be observed. Similar observations have been made by Minot and Murphy in patients with pernicious anemia.

## SUMMARY AND CONCLUSIONS

In a study of the treatment in 126 cases of anemia due to various causes, the following facts were evident:

1. The recovery from anemia due to chronic loss of blood may be accelerated following the administration of liver and iron. In some cases, transfusion of blood was necessary owing to the severity of the anemia. Continued loss of blood in small amounts and sepsis retard recovery.

2. Anemias resulting from inadequate or faulty diets were often associated with the avitaminoses or other deficiency disorders. Many of these patients recovered following a well balanced diet, and in some regeneration of the hemoglobin was accelerated by the use of liver or iron.

3. The anemia associated with chronic dysentery usually appeared in patients who had been on inadequate diets, and who had had active dysentery for two months or longer. Hemorrhage, infection and gastric anacidity played a minor rôle in the production of the anemia. In the group as a whole, all of the clinical features that are said to be characteristic of pernicious anemia were observed, including atrophy of the lingual papillae, subacute combined sclerosis, gastric anacidity and anemia responding to liver extract. These observations lend support to the hypothesis that pernicious anemia is a deficiency disease.

4. Anemia associated with infestation due to hookworm may be cured with iron, or liver and iron, while the patients continue to carry the worms. Malnutrition and faulty diets are important factors in predisposing such patients to anemia.

5. Women with the anemias of pregnancy recover following the transfusion of blood or following the administration of liver and iron. In some cases, iron alone is positive; in others, liver or liver extract is potent in increasing the rate of recovery.

6. Recovery from the anemia associated with kala-azar may be extremely slow in spite of treatment with antimony compounds, transfusions of blood and ingestion of liver and iron. In this condition it appears as if the damage to the bone marrow were responsible for the anemia.

7. When recovery occurred in many of the foregoing types of anemia, the reticulocytes were increased. Generally speaking, the number of reticulocytes depends on the level of the red cell count at the beginning of the treatment, although there were exceptions in cases in which one observed relatively large increases in reticulocytes with a high red blood cell count. In most of these cases the hemoglobin content was low. In other cases an increase in the reticulocytes was not observed following treatment. In some of these cases the reticulocytes had been increased before treatment was begun; in others, they were never increased.

8. When liver ash was given in amounts equivalent to 300 Gm. of whole liver a day, containing 21 mg. of iron, striking results were not observed. In several instances, there was a moderate increase in the hemoglobin, red blood cells and reticulocytes, and this response was usually observed in patients who subsequently recovered promptly on larger doses of iron.

9. In some cases of anemia, liver and iron were more effective than when either one was given alone. In others, the maximum effect was observed following the use of iron.

10. Liver extract was of demonstrable value in some of the nutritional anemias of childhood, some of the anemias associated with preg-

nancy and in chronic dysentery. It was of little value in posthemorrhagic anemia.

11. From our observations, it was not possible to predict in every case which form of treatment would be most beneficial. If complete recovery is not observed in patients following the use of iron, liver should be added. In many patients who do not respond to liver or iron, there is usually an adequate cause to explain their failure. Infection and pathologic processes of the bone marrow are of the greatest importance. The response in the various clinical anemias following the ingestion of food substances other than liver, kidney or iron needs further investigation.

# METABOLISM IN MYOTONIA ATROPHICA

## REPORT OF A CASE *

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AND
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OMAHA

Myotonia atrophica or dystrophica is one of the rarer forms of myopathy, which, in addition to the typical myotonia, is characterized by the following conditions: (1) onset usually in the third decade; (2) limitation of the myotonia to special groups of muscles, namely, those of the hands, the tongue and the legs; (3) typical distribution of the atrophy to the face, the sternocleidomastoid muscles, the hand and the forearm and the muscles of the leg; (4) general emaciation; (5) baldness; (6) testicular atrophy; (7) cataract; (8) defect in speech; (9) combination with ataxia and Westphal's sign.[1]

The etiology of this disease is obscure. Naegeli [2] regarded the pathogenesis of the disease as originating in a polyglandular disturbance, presumably with a marked hereditary predisposition. This relation to endocrine involvement was also assumed by Barkman [3] and others, though the evidence for this is more circumstantial than direct. The occurrence of primary cataracts, testicular atrophy or hypogenitalism in the female, together with atrophic changes in the skin, is usually cited as favoring an assumption of glandular disturbance as the basis of this peculiar condition, which manifests itself in an increased and persistent tonus of the flexor muscles, particularly those of the extremities and of the face.

### REPORT OF A CASE

*History.*—Mr. R. R., aged 28, who was born in America of Swedish parents, first noted the development of progressive muscular weakness following an inguinal herniotomy on the left side, which was performed in 1926. This operation was followed by atrophy of the left testis. When the patient entered the University Hospital in February, 1930, the musculature in the limbs and also in the face and neck was greatly reduced, giving him the typical "hatchet face," "polelike neck" and "pipestem extremities" of patients with myotonia. He had lost the knee

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* From the Department of Biochemistry and the University Hospital, University of Nebraska College of Medicine.

1. Curschmann, H.: Deutsche Ztschr. f. Nervenh. **45**:161, 1912.
2. Naegeli: München. med. Wchnschr. **64**:1631, 1917.
3. Barkman, A.: Acta med. Scandinav. **56**:686, 1922.

jerk, and the atrophy of the legs was advanced far enough to produce drop foot and the characteristic steppage gait. The ability to relax the muscles was considerably diminished, which was well shown in the difficulty he experienced in letting go after gripping something with his hand.

He had lost only about from 7 to 8 pounds (3.2 to 3.6 Kg.). The Wassermann test gave negative results, and the past history was unimportant, except for some diseases of childhood, influenza and a mild attack of smallpox in 1918. The family history gave no evidence of a possible hereditary etiology.

Ophthalmoscopic examination showed fine opacities in the lens, more marked at the periphery. Examination of the blood showed 4,680,000 red cells, 7,000 white cells and 85 per cent hemoglobin. Studies on the basal metabolism repeated on two occasions showed rates of —13 and —14 per cent, respectively.

Urinalysis gave negative results for albumin and sugar.

The analysis of the blood made on two different occasions gave the results shown in table 1.

In addition to the determinations made on the whole blood, the calcium serum was found to be 11 mg. per hundred cubic centimeters and the inorganic phosphorus, 3.5 mg.

TABLE 1.—*Results of Analysis of the Blood of a Patient with Myotonia Atrophica*

| | First Analysis, Mg. per 100 Cc. | Second Analysis, Mg. per 100 Cc. |
|---|---|---|
| Nonprotein nitrogen | 39.0 | 34.0 |
| Sugar | 90.0 | .... |
| Creatinine | 1.5 | 1.7 |
| Creatine | .... | 4.2 |
| Uric acid | .... | 4.4 |
| Lactic acid | .... | 36.9 |

In view of the fact that even mild excitation would cause the lactic acid of the blood to rise above the normal level, nothing in the chemical picture of the blood of the patient threw any light on the pathogenesis of the condition.

For nearly a month the patient was kept on a carefully controlled diet during which the creatine-creatinine excretion was studied.[4] The specimens of urine were collected for every twenty-four hours and preserved with thymol. The specimens were analyzed for the total content of nitrogen, creatinine, creatine and uric acid. Organic acids were determined by the Van Slyke-Palmer method and also by the recent modification of this procedure by Greenwald.[5]

The diet specially prepared in the kitchen of the hospital was selected so that equilibrium in the nitrogen content was maintained throughout the experiment, and the patient retained his weight of 57 Kg. unchanged. This diet, consisting of about 60 Gm. of protein, 160 Gm. of carbohydrate and 120 Gm. of fat, furnished about 2,000 calories daily. The protein was given largely (60 per cent) as meat, but during some periods this was replaced by eggs and cheese in equivalent amounts. During one period, this moiety of the protein was furnished by gelatin.

The results of this metabolic study are summarized in table 2. The excretion of nitrogen was fairly constant from day to day, and, except during the days

4. Miss Fritschel, the dietitian, personally supervised the patient's dietary throughout the whole experiment.

5. Greenwald, I.: J. Biol. Chem. **85**:447, 1930.

TABLE 2.—*Results of Study on Metabolism Made on a Patient with Myotonia Atrophica*

| Date | Duration of Period, Days | Total Output of Urine, Cc. | Daily Urinary Excretion, Gm. | | | | | Nitrogen Partition, in per Cent of Total | | | Percentage of Total Creatinine as Creatine | Tenth-Normal Organic Acid, CC. | | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Total Nitrogen | Creatinine | Creatine | Creatinine and Creatine | Uric Acid | Creatinine Nitrogen | Creatine Nitrogen | Uric Acid Nitrogen | | Van Slyke Test | Greenwald Test | |
| March 10-13 | 3 | 2,830 | 7.87 | 0.795 | 0.703 | 1.498 | 0.909 | 3.73 | 3.30 | 3.85 | 46.9 | 294 | 225 | 150 Gm. of carbohydrate, 119 Gm. of fat and 62 Gm. of protein (36 Gm. of meat protein) |
| March 13-16 | 3 | 3,880 | 6.32 | 0.725 | 0.562 | 1.287 | 0.703 | 3.70 | 3.28 | 3.70 | 43.7 | 374 | 272 | 153 Gm. of carbohydrate, 120 Gm. of fat and 60 Gm. of protein (no meat protein) |
| March 16-19 | 3 | 3,860 | 7.19 | 0.717 | 0.353 | 1.070 | 0.710 | 3.69 | 1.81 | 3.30 | 33.0 | 347 | 262 | 163 Gm. of carbohydrate, 120 Gm. of fat and 59 Gm. of protein (no meat protein) |
| March 19-22 | 3 | 2,950 | 6.94 | 0.775 | 0.595 | 1.370 | 0.667 | 3.77 | 4.12 | 3.20 | 43.4 | 294 | 240 | 167 Gm. of carbohydrate, 118 Gm. of fat and 62 Gm. of protein (36 Gm. of meat protein) |
| March 22-23 | 1 | 1,570 | 6.28 | 0.965 | 1.390 | 2.355 | 0.880 | 5.67 | 8.17 | 4.67 | 61.2 | 295 | 273 | 192 Gm. of carbohydrate, 121 Gm. of fat and 65 Gm. of protein (34 Gm. of meat protein) |
| March 23-24 | 1 | 1,000 | 5.16 | 0.788 | 1.342 | 2.130 | 0.900 | 5.63 | 9.60 | 5.81 | 63.0 | 273 | 266 | 160 Gm. of carbohydrate, 121 Gm. of fat and 60 Gm. of protein (35 Gm. of meat protein) |
| March 24-25 | 1 | 1,220 | 6.85 | 1.031 | 1.601 | 2.632 | 0.880 | 5.55 | 8.77 | 4.28 | 60.8 | 270 | 259 | 164 Gm. of carbohydrate, 121 Gm. of fat and 62 Gm. of protein (34 Gm. of meat protein) |
| March 26-29 | 3 | 2,750 | 6.54 | 0.769 | 0.458 | 1.227 | 0.903 | 4.34 | 2.58 | 4.61 | 37.3 | 340 | 287 | 161 Gm. of carbohydrate, 124 Gm. of fat and 63 Gm. of protein (36 Gm. of meat protein) |
| April 1-3 | 2 | 2,100 | 7.89 | 0.840 | 0.608 | 1.448 | 0.834 | 3.93 | 2.84 | 3.53 | 42.0 | 339 | 303 | 165 Gm. of carbohydrate, 121 Gm. of fat and 61 Gm. of protein (35 Gm. of meat protein) |
| April 3-6 | 3 | 3,240 | 8.28 | 0.645 | 0.533 | 1.178 | 0.673 | 2.87 | 2.88 | 2.71 | 45.3 | 340 | 288 | 164 Gm. of carbohydrate, 122 Gm. of fat and 61 Gm. of protein (no meat; 35 Gm. of gelatin protein) |
| April 6-8 | 2 | 2,115 | 7.58 | 0.815 | 0.568 | 1.383 | 0.948 | 3.97 | 2.77 | 4.17 | 41.0 | 332 | 238 | 164 Gm. of carbohydrate, 123 Gm. of fat and 63 Gm. of protein (36 Gm. of meat protein) |

when creatine was administered, the amount averaged about 7.3 Gm. During the twelve days of the preliminary study (fore-periods), though during half of this time no meat was consumed, the output of creatinine nitrogen was practically unchanged, constituting about 3.72 per cent of the total urinary nitrogen. The average daily excretion of creatinine was 0.753 Gm. During the last ten days of the experiment (after-periods), the daily variations were somewhat greater, but the creatinine nitrogen still constituted 3.78 per cent of the total excretion of nitrogen. The creatinine coefficient of our patient, being 13.4 mg. per kilogram of weight, is definitely low for the age of the patient and approaches more nearly that of a child. However, the patient showed persistent creatinuria and, if the total elimination of creatinine is taken into consideration, the total daily excretion of 23 mg. per kilogram of body weight is an entirely normal coefficient for a person of that age. Therefore, it would seem that the chief abnormality of the creatine-creatinine metabolism of the patient was the inability to convert creatine to creatinine. Thus, part of the creatine, about 43 per cent, appeared in the urine unchanged, but the metabolism of the total amount of creatine was not appreciably affected.

The exogenous origin of some of the urinary creatine is obvious when one compares the results of a diet in which meat was the essential source of protein with those of a diet in which creatine-free foods were substituted for the meat. The decrease in the creatinuria during the second, and especially during the third, fore-period is notable. However, the feeding of a protein rich in arginine (gelatin), which was done in the period from April 3 to April 6, had no influence on the output of either creatinine or creatine, which had actually diminished during that period.

Having established definitely during a preliminary study extending over twelve days the creatine-creatinine excretion of the patient, we gave him 1.32 Gm. of creatine-hydrate, equivalent to 1 Gm. of creatinine, by mouth on three consecutive days. The excretion of creatine on those days was greatly increased, constituting nearly 62 per cent of the total creatinine content in the urine. During the first day, 1.049 Gm. of extra creatinine was excreted in the urine, of which 20 per cent was in the form of extra preformed creatinine. During the second day, for an undetermined cause, unless the reduced output of urine may be considered responsible, only a little more than 80 per cent of the ingested creatine had been eliminated, a much smaller proportion of which (less than 5 per cent) was in the form of extra creatinine. This retention, however, was only temporary and was fully accounted for by the creatine eliminated in the next twenty-four hour period. In this third period, again, about 20 per cent of the total extra excretion was in the form of preformed creatinine. Taking 0.753 Gm. as the average daily excretion of creatinine, the average excretion on the three days when creatine was fed (0.928 Gm.) showed an increase of 0.175 Gm., or 23.2 per cent, per day. The daily excretion of creatine likewise increased from 0.553 Gm. to 1.444 Gm., or 0.891 Gm. The increase in the total excretion of creatinine resulting from feeding creatine equivalent to 1 Gm. of creatinine was thus 1.066 Gm. In other words, the creatine fed is recovered in the urine eliminated within a period of twenty-four hours, whereby 16.6 per cent seems to be converted to creatinine, while 83.4 per cent is eliminated unchanged.

We purposely limited the oral administration of creatine so as not to overtax the organism's ability to metabolize it, but even such a small amount was eliminated practically quantitatively in the course of the day, and had no effect on the creatine-creatinine excretion in subsequent periods. The excretion of uric acid was somewhat increased during the days when creatine was fed. Probably

the most striking effect was shown by the study of the excretion of organic acids. Although the results do not permit us to draw any definite conclusion as to the influence exerted by the feeding of creatine on the absolute amount of organic acid in the urine, a distinct difference appears when the organic acids are determined either by the Van Slyke-Palmer method or by the Greenwald [5] modification of that method. The results obtained by these two procedures varied considerably. But whereas during the twelve days of the fore-period and the ten days of the after-period the difference in the daily excretion of organic acid, as determined by these two methods, averaged between 78 and 59 cc. of tenth-normal acid, respectively, during the three days when the creatine was fed, the difference was only 13 cc.

## COMMENT

The persistent creatinuria observed in our patient is similar to that described in several other cases of myopathy. Levene and Kristeller [6] found creatinuria in patients with muscular dystrophy, and Bodansky, Schwab and Brindley [7] in a case of myositis fibrosa. However, Bürger [8] found a much less pronounced creatinuria in his several patients on a strictly creatine-free diet.

In view of the diminution in the excretion of creatinine, the coefficient for creatinine, as observed by Gibson, Martin and Buell [9] and others, likewise tends to become very low. However, the coefficient for the total creatinine content, as we have determined for our patient, may actually remain normal in spite of the fact that the coefficient for preformed creatinine is unusually low. Indeed, Bürger [8] maintained that the coefficient for the total creatinine content is low only in patients whose musculature is undergoing massive reduction, as in progressive dystrophy, which serves to differentiate this disease from various other types of myopathy in which the coefficient for the total creatinine content remains high or practically normal.

The outstanding fact in this study was the inability of the patient with myotonia atrophica to retain and to store exogenous creatine. In the normal adult, small doses of administered creatine are completely retained, as shown by the work of Folin,[10] Myers and Fine,[11] and Rose and Dimmitt.[12] Our patient, however, was unable to retain a similar dose of creatine, and it was eliminated quickly through the urine.

6. Levene, P. A., and Kristeller, L.: Am. J. Physiol. **24**:45, 1909.

7. Bodansky, M.; Schwab, E. H., and Brindley, P.: J. Biol. Chem. **85**:307, 1929.

8. Bürger, M.: Ztschr. f. d. ges. exper. Med. **9**:361, 1919.

9. Gibson, R. B.; Martin, F. T., and Buell, M.: A Metabolic Study of Progressive Pseudohypertrophic Muscular Dystrophy and Other Muscular Atrophies, Arch. Int. Med. **29**:82 (Jan.) 1922.

10. Folin, O.: Festskr. f. Olof Hammarsten, Upsala läkaref. Förh., 1906, pt. 3.

11. Myers, V. C., and Fine, M. S.: J. Biol. Chem. **21**:377, 1915.

12. Rose, W. C., and Dimmitt, F. W.: J. Biol. Chem. **26**:345, 1916.

This inability to fix creatine has been noted in various conditions involving the muscular system. Thus, Powis and Raper [13] and Ziegler and Pearce [14] found the same condition in children with amyotonia congenita; Gibson and Martin,[15] in a woman with pseudohypertrophic dystrophy, and Bodansky and his associates,[7] in a boy 15 years of age afflicted with generalized myositis fibrosa. Present knowledge of the existence in muscle of a labile compound of creatine with phosphoric acid, which hydrolyzes readily in the course of muscular activity and is again resynthesized, and its important rôle in muscular activity suggest that the inability of diseased muscles to retain or even to store temporarily the exogenous creatine may be associated with their inability to form this phosphagen compound.

In our patient the feeding of creatine called forth a definite and considerable rise in the urinary output of creatinine, as much as 16.6 per cent of the ingested creatine having been eliminated after conversion to creatinine. It is generally recognized that such conversion takes place in the muscles, which suggests, at least as a strong probability, that the mechanism for the creatine-phosphoric acid synthesis and the mechanism for the creatine-creatinine transformation in muscles are independent of each other. In view of the fact that the experimental work from the Meyerhof school has shown that the synthesis of phosphagen is closely tied up with the glycogen metabolism of the muscle, it would seem that the inability of the affected muscles to retain creatine is ultimately to be correlated with the more fundamental disturbance in the glucid metabolism and the lack of glycogen.

## SUMMARY AND CONCLUSION

1. In a patient with myotonia atrophica, whose diet was carefully controlled, a persistent and marked creatinuria was present, even when a practically creatine-free diet was used.

2. Feeding gelatin as the principal source of protein did not affect the amount of creatine eliminated in the urine.

3. Calculated on the basis of the total amount of creatinine excreted, the coefficient for creatinine had a normal value, though the coefficient for preformed creatinine was very low.

4. The concentration of creatine and creatinine in the blood of this patient was entirely within the normal range. In fact, chemical analysis of the blood revealed nothing unusual.

13. Powis, F., and Raper, H. S.: Biochem. J. **10**:363, 1916.

14. Ziegler, M. R., and Pearce, N. O.: J. Biol. Chem. **42**:581, 1920.

15. Gibson, R. B., and Martin, F. T.: J. Biol. Chem. **49**:319, 1921.

5. A study of the excretion of uric acid and organic acid disclosed no significant facts.

6. Administered creatine is quickly and quantitatively eliminated through the urine, about 84 per cent of the ingested creatine appearing unchanged and 16 per cent appearing as creatinine.

7. The results of this experimental study indicate that the transformation of creatine to creatinine by the atrophied muscles is not affected, but that they are apparently unable to retain and synthesize creatine to phosphagen. The suggestion is made that the inability of the atrophied muscles to synthesize phosphagen, which was the most outstanding peculiarity of the metabolism of our patient, is associated with the more fundamental disturbance in the metabolism of glycogen of the muscles.

# TUBERCULOUS MENINGITIS WITH SYPHILITIC MENINGITIS TERMINATING IN RECOVERY

## A REVIEW OF THE LITERATURE*

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Tuberculous meningitis has been looked on as a disease that must end disastrously. This fact, unfortunately, has been emphasized so frequently that when one mentions a case that terminated in recovery, not only is the diagnosis automatically challenged, but there is a tendency to discard all the positive observations and question the laboratory technic. However, a perusal of the literature on this subject will convince the most pronounced skeptic that there is no law in the science of medicine that disbars the meninges from localizing and overcoming an infection of the tubercle bacillus, and that some patients do recover from this disease. If tuberculosis of other tissues and organs may subside, then why not tuberculosis of the meninges? No doubt recoveries are rare, but the fact that some cases do terminate favorably should be recognized. Because of the rarity of this unexpected result, we are presenting the following case.

### REPORT OF CASE

*History.*—A colored man, aged 29, was admitted to the hospital on July 3, 1928, complaining bitterly of severe pains in the head. The family history was irrelevant. The patient had had gonorrhea in 1918 and a chancre in 1920. There was no history of pleurisy. The present illness dated back four days when the patient complained of a headache beginning in the frontal region, with sharp pains going around the head and down the neck. The frontal pain was sharp, shooting and continuous. Dizziness, ringing in the ears and diplopia were present at the onset. The patient was nauseated but did not vomit until the third day of his illness. He had been coughing for several months and occasionally had had blood-streaked sputum.

*Examination.*—Examination revealed that the patient was fairly well nourished and well developed. The expression of the face was indicative of acute pain. The eyelids were tightly brought together to shut out the light. The pupils were irregular and reacted sluggishly to light; the right eye was turned inward; there was no ptosis of the lids. The neck was rigid; a few small glands were palpable. The heart sounds were regular but somewhat impaired; no murmurs were heard. Percus-

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* From the Medical Department, Jefferson Medical College, and the Medical Service of Dr. S. A. Lowenberg, Philadelphia General Hospital.

sion was impaired over the upper part of the chest on the right side; the breath sounds were harsher than normal and were bronchovesicular; a few scattered râles could be heard in this area. There was a generalized rigidity of the abdominal walls with a fairly marked hyperesthesia; the liver and spleen were not enlarged on percussion. Examination of the extremities showed that Kernig's and Brudzinki's signs were positive on both sides; Babinski's sign could not be elicited. The spinal fluid was examined and about 50 cc. was removed; there was apparently no increase in pressure; the fluid was cloudy; there were no organisms; the cell count was 1,200, 56 per cent being polymorphonuclears and 44 per cent lymphocytes. The blood count showed 4,900 leukocytes, 51 per cent polymorphonuclears, 44 per cent lymphocytes, 2 per cent eosinophils and 1 per cent basophils. The blood sugar was 75 mg. per hundred cubic centimeters of blood, and the urea was 14 mg. The temperature was 100 F.; the pulse rate, 96, and the respiratory rate, 32.

*Treatment and Course.*—The following notes of the patient's progress were made:

July 6, 1928: The general condition was worse; the patient was irrational; the limbs were spastic. About 40 cc. of a greenish-yellow spinal fluid was removed, under pressure; examination for evidences of tuberculosis gave negative results. The temperature was 99 F.; the pulse rate, 90, and the respiratory rate, 30. The Wassermann reaction of the blood was 4 plus, with all antigens. A diagnosis of syphilitic meningitis was made.

July 7: Thirty grains (1.95 Gm.) of sodium iodide was given intravenously. The spinal fluid had a cloudy yellowish appearance. The general condition of the patient was much improved.

July 8: The general condition was fair. Thirty grains of sodium iodide was given intravenously. A spinal tap was performed and 30 cc. of spinal fluid removed under pressure.

July 10: The condition was gradually improving. The temperature was 98.4 F; the pulse rate, 92, and the respiratory rate, 24. Thirty grains of sodium iodide was given intravenously.

July 11, 12 and 13: The patient was given 10 cc. of Pregl's iodine solution intravenously. The temperature, pulse and respirations were normal.

July 14, 15 and 16: The patient complained of headache; he did not feel well and seemed much weaker. The temperature was 101 F.; the pulse rate, 100, and the respiratory rate, 30. On spinal tap, the fluid was clear. Examination of the spinal fluid at this stage showed a positive Levinson reaction and the formation of a pellicle. *Tubercle bacilli were found in the pellicle.* The use of iodides was discontinued.

July 17: The patient complained of intense headache; he was much weaker and was in a semistuporous condition. The temperature was 101 F.; the pulse rate, 120; and the respiratory rate, 30.

July 20: The condition was much improved. The patient insisted on sitting up in bed. His appetite was good. The rigidity of the neck had subsided, but Kernig's sign was still present. Under slight pressure, spinal tap revealed a clear fluid; the cell count was 26; there was a faint trace of globulin. The temperature was 98.4 F.; the pulse rate, 90, and the respiratory rate, 25.

Neurologic Consultation (report by Dr. B. Weiss): The pupils were irregular; they reacted sluggishly to light; there was palsy on both sides. The tongue protruded in the midline; there was no tremor. The lips puckered well. There was some rigidity of the neck. The power in the upper extremities was fair. There was no tremor of the extended hand. The reflexes of the biceps muscles were normal; those of the triceps muscles were diminished on the left. The abdominal

reflexes were normal. The knee jerks and the achilles tendon reflex were absent bilaterally. There was a positive bilateral Kernig sign. There was no clonus or Babinski sign. General slight hyperesthesia was present. Somnolence was also noted. The patient was mentally clear.

Observations of tubercle bacilli in the pellicle led to a diagnosis of tuberculous meningitis. The presence of greenish-yellow pus associated with an increase in polymorphonuclears in the spinal fluid suggested a superimposed purulent meningitis. A complete examination of the sinus and transillumination were advised to determine, if possible, the initial foci of infection.

The history of initial chancre with typical Argyll Robertson pupils and absent achilles tendon reflexes and knee jerks and the history of vesical disturbance and of sharp lancinating pains which the patient termed rheumatic, together with serologic observations, indicated a specific meningomyelitis with particular involvement of the posterior columns. The acuteness of the onset ruled out a purely tabetic involvement.

Ocular Examination (Dr. O'Brien): The media were clear; the disks were oval. The edges were blurred, and the veins were overfull. There were no other pathologic conditions. The examination was made without mydriasis.

July 23: The patient had been doing fairly well. On that day he complained of severe pains in the left side of the neck. The temperature rose to 104 F, the pulse rate to 116 and the respiratory rate to 35. Examination revealed marked tenderness in the left side of the neck with swelling. Thirty cubic centimeters of clear spinal fluid was removed without pressure. Laboratory examination of the fluid gave negative results.

July 25: The spinal fluid showed a cell count of 105, with a faint trace of globulin; the Levinson reaction was positive. The temperature had subsided to normal and then rose to 101 F.

July 27: There was a sharp rise in temperature to 105 F.; the pulse rate rose to 130 and the respiratory rate to 34. The patient was uncomfortable; he had difficulty in swallowing and complained of severe pains in the left side of the neck. Surgical consultation was requested. An examination was made by Dr. Righter, who diagnosed the condition as acute cervical adenitis.

Thirty cubic centimeters of spinal fluid was removed under slight pressure. Laboratory examination gave negative results for tubercle bacilli and for the formation of a pellicle.

July 30: The condition had subsided completely. The temperature, the pulse rate and the respiratory rate were normal. The patient felt much better.

July 31: The general condition was good; the patient was improving and was able to sit in a chair. There was no complaint of pain. However, there was still a slight rigidity of the neck.

August 14: The patient was discharged apparently in good condition. The temperature, pulse rate and respiratory rate had been normal for three weeks. When he was discharged, a diagnosis of syphilitic and tuberculous meningitis was made.

October 7: The patient reported for observation; he was feeling well. He complained of some irritability of the bladder. The spinal fluid was examined: there were no cells and no increase in globulin. The Wassermann test gave negative results with both antigens. The colloidal gold curve was normal. The Levinson test, however, gave positive results.

Autopsy was performed on a guinea-pig that had been inoculated with the spinal fluid; the result was negative for tubercles. The autopsy was done approximately three months after the original inoculation.

The following year the patient felt well. An attempt was made to have him return to check up the studies of the spinal fluid, but he declined.

In the spring of 1930, an attempt was made to communicate with the patient for further observations. He had left town, but we were informed by a sister that he was living and feeling well.

Table 1 shows at a glance the observations on the spinal fluid.

TABLE 1.—*Analyses of the Cerebrospinal Fluid*

| Date, 1928 | Appearance | Cell Count | Polymorphonuclears | Lymphocytes | Globulin | Wassermann Reaction | Colloidal Gold Curve | Levinson Reaction | Pellicle | Tubercle Bacilli | Sugar, Mg. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 7/ 3 | Cloudy | 1,200 | 56 | 44 | Heavy trace | + | 1233342211 | ..... | ..... | ..... | 30 |
| 7/ 4 | Cloudy, opalescent | 500 | .. | .. | Trace | .. | ..... | ..... | ..... | ..... | .. |
| 7/ 5 | Cloudy | 1,500 | 80 | 20 | Trace | .. | ..... | Negative | ..... | ..... | .. |
| 7/ 6 | Cloudy | 3,750 | 93 | 7 | Heavy trace | ++++ | ..... | Negative | Negative | ..... | .. |
| 7/ 7 | Yellowish, cloudy | 1,303 | .. | .. | Trace | .. | ..... | ..... | ..... | ..... | .. |
| 7/ 8 | Cloudy | 2,500 | 83 | 17 | ..... | + | 2333433222 | ..... | ..... | ..... | .. |
| 7/ 9 | Slightly turbid | 99 | .. | .. | Trace | .. | ..... | ..... | ..... | ..... | .. |
| 7/10 | Cloudy | 82 | .. | .. | Faint trace | .. | ..... | ..... | ..... | ..... | .. |
| 7/11 | Slightly cloudy | 283 | .. | .. | Trace | Negative | ..... | ..... | ..... | ..... | 37 |
| 7/12 | Clear | 250 | .. | .. | Trace | .. | ..... | ..... | ..... | ..... | .. |
| 7/13 | Clear | 150 | .. | 100 | Trace | ++ | ..... | ..... | ..... | ..... | .. |
| 7/14 | Clear | 250 | 19 | 75 | ..... | .. | ..... | Positive | Present | Present | .. |
| 7/16 | Clear | ..... | .. | .. | ..... | .. | ..... | Positive | Present | Negative | .. |
| 7/17 | Clear | ..... | .. | .. | ..... | ++ | ..... | ..... | Present | ..... | .. |
| 7/20 | Clear | 26 | .. | .. | Faint trace | .. | ..... | ..... | Present | ..... | .. |
| 7/21 | Clear | 10 | .. | .. | Faint trace | ++++ | ..... | ..... | None | None | .. |
| 7/23 | Clear | 0 | .. | .. | 0 | .. | ..... | ..... | ..... | ..... | .. |
| 7/24 | Clear | 0 | .. | .. | 0 | .. | ..... | ..... | Small | None | .. |
| 7/25 | Clear | 105 | .. | .. | Faint trace | .. | ..... | Positive | ..... | ..... | .. |
| 7/26 | Clear | 72 | .. | .. | Faint trace | .. | ..... | ..... | None | ..... | .. |
| 7/27 | Clear | 7 | .. | .. | Very faint trace | .. | ..... | ..... | None | None | .. |
| 7/30 | Clear | 6 | .. | .. | Faint trace | .. | ..... | ..... | None | None | .. |
| 10/7 | Clear | 0 | .. | .. | 0 | Negative | 0000000000 | Positive | None | None | .. |

## COMMENT

From the history and symptoms of the case, we were unquestionably dealing with some form of meningitis, the exact etiologic diagnosis demanding consideration. In the absence of micro-organisms, which

could not be demonstrated either by staining or by culture, that is, in the early course of the disease, we were inclined to consider it a meningitis other than the well recognized forms, such as meningococcic, pneumococcic or influenzal. The strongly positive Wassermann reactions in both the spinal fluid and the blood, the high cell count, the colloidal gold curve and the moderate range in temperature plus the negative observations already mentioned warrant a diagnosis of syphilitic meningitis. This diagnosis conforms with the symptoms and the laboratory studies usually found in syphilis of the central nervous system with meningeal involvement as mentioned by Stokes.[1]

The patient was treated accordingly with iodides both by mouth and intravenously and with mercurial inunctions. Spinal punctures were performed daily for relief from the symptoms and for observations on the course of the disease. The patient gradually improved during the first week; the temperature, pulse and respirations subsided and reached normal limits by the tenth day. Shortly afterward, however, there was a change in the patient's condition. He complained of intense headaches and marked weakness. There was a rise in temperature with a corresponding increase in the pulse and respiratory rates. The laboratory studies of the spinal fluid were as follows: the fluid was clear, the cell count was 250, the Levinson reaction was positive, formation of pellicle was present and on examination of this pellicle, tubercle bacilli were definitely found by Dr. Walter J. Crocker, chief clinical pathologist, who reported that "in three different fields, beaded acid-fast rod-shaped bacilli were found" which he believed were tubercle bacilli. The Ziehl-Neelsen acid-fast method was used in staining.

With these laboratory observations, a diagnosis of tuberculous meningitis was made, and the usual unfavorable prognosis was given. The patient was uncomfortable for several days. Subsequently, however, there was an unexpected improvement and a decided change in the spinal fluid. Within six or seven days, he had recovered sufficiently to insist on sitting in a chair. The rigidity of the muscles in the back of the neck had subsided but Kernig's sign was still present. Except for an attack of acute cervical adenitis, he made an uneventful recovery, and he was discharged from the hospital six weeks after his admission. The final diagnosis was syphilitic meningitis with tuberculous meningitis terminating in recovery.

Assuming that the diagnosis is correct, the next question to decide is what constitutes an authentic case and how does this case measure up with the required specifications. Whether or not we are justified in labeling this case tuberculous meningitis entails some discussion.

1. Stokes, John H.: Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1926, p. 925.

This question has been thoroughly discussed in various contributions on the subject by Martin,[2] Pitfield,[3] Cramer and Bickel,[4] Borruso [5] and others. The concensus indicates that the significant and convincing observations are: (1) the formation of a pellicle with the demonstration of tubercle bacilli in the fluid; (2) postmortem examination showing evidences of an old meningitis which has healed; (3) inoculation of the spinal fluid into a guinea-pig, followed by the development of tuberculosis. Other collateral observations that may assist in arriving at a diagnosis of tuberculous meningitis are cytodiagnosis of the fluid, lymphocytosis usually being present, one must not forget, however, that there may be exceptions to this rule, as polymorphonuclearcytosis is found occasionally; tubercles in the choroid; evidences of tuberculosis elsewhere in the body; the Levinson test of the spinal fluid; reduction of chlorides, and the tuberculin test.

It would be unreasonable to expect all of the aforementioned requirements to be present in every case. The demonstration of tubercle bacilli in the spinal fluid has been accepted as fairly conclusive evidence of a positive diagnosis of tuberculous meningitis. In our case, these organisms were definitely found, the formation of pellicle was noticed on several occasions; the Levinson reaction was positive; there was suggestive evidence of involvement of the lungs, and cervical adenitis was present. All of these symptoms seem to warrant a diagnosis of tuberculous meningitis. The fact that the organisms were found only once may cast some doubt on the diagnosis. Some authorities on tuberculosis, particularly when dealing with the pulmonary form, insist on more than a single report confirming the presence of tubercle bacilli, realizing as they do, that in the examination of specimens of sputums an error may be made in the laboratory. However, the examination of spinal fluids requires more skill and care. As a rule, in laboratories such examinations are performed only by those who are well trained for this type of work. In our case, the positive observation of the tubercle bacilli was confirmed by the chief of the laboratory and others who were present. The presence of the organisms in the spinal fluid was unquestionably established. The failure to demonstrate the bacilli in other specimens of spinal fluid from this case may or may not be significant. We do not know exactly how the micro-

2. Martin, Alfred E.: The Occurrence of Remissions and Recovery in Tuberculous Meningitis; A Critical Review, Brain **32**:209, 1909.

3. Pitfield, R. I.: Recovery from Tubercular Meningitis, with Report of Cases, Am. J. M. Sc. **146**:37, 1913.

4. Cramer, A., and Bickel, G.: La méningite tuberculeuse, est-elle curable? Ann. de méd. **12**:226, 1922.

5. Borruso, G.: Curability of Tuberculous Meningitis, Policlinico (sez. med.) **36**:493, 1929.

organisms get into the spinal fluid, nor do we understand whether or not this is a daily performance. Is it not likely that only on certain occasions the tubercle bacilli work their way through the lymphatic glands and get into the cerebrospinal fluid, and that if one happens to obtain the spinal fluid on that particular day and has the studies made by a trained examiner one will obtain a positive report? On the other hand, it is not unusual to obtain negative reports on the spinal fluid in cases in which inoculation into guinea-pigs produced tuberculosis, and it is not unusual to have negative spinal fluids in cases in which the diagnosis is proved by autopsy. Another explanation for this discrepancy, if we may call it such, is the fact that only a limited number of the bacilli were free in the circulation and the spinal fluid. This fact likewise enters in the possible explanation for the recovery in these cases and is discussed under that heading. The weak link in the chain was the failure to produce tuberculosis on inoculation of the spinal fluid into a guinea-pig after a period of three months. This negative observation, however, does not seem significant enough to nullify the positive evidence because it is possible that the tubercle bacilli were not present in sufficient number to infect the animal. Sometimes the animal is killed before the disease has time to develop. Bezançon and Gastinet [6] and Tilli [7] reported inoculations of guinea-pigs requiring fourteen and thirty months, respectively, before the disease appeared in the animals, they suggested that the possible explanation was a diminished virulence of the organisms.

An interesting angle to the discussion of the diagnosis in this case is the question of syphilis. Were we dealing with a bona fide case of syphilitic meningitis in the beginning, which later proved to be fertile soil for a temporary involvement of tubercle bacilli or was it primarily a case of tuberculous meningitis with positive serologic reactions, as reported recently by Schaffle and Riesenberg? [8] In their contribution they found that occasionally the spinal fluid may show a strongly positive Wassermann reaction in nonsyphilitic meningitis. Their series consisted of 8 cases, 5 of which were tuberculous meningitis. The Wassermann reaction of the blood was negative in each case. However, the possibility of the development of tuberculous meningitis in a syphilitic person must be borne in mind. Despite the fact that other forms of tuberculosis are prone to develop in syphilitic persons, the combination of syphilis and tuberculous meningitis is strikingly infre-

6. Bezançon and Gastinet, quoted by Cramer and Bickel, p. 238 (footnote 4).

7. Tilli, P.: Meningite tubercolare; tentativi di cura con Reiniezioni sottocute del liquido cefalo-rachidiano del paziente, Policlinico (sez. prat.) **23**:1357, 1916.

8. Schaffle, K., and Riesenberg, M.: The Occurrence of Positive Wassermann Reactions in the Spinal Fluid of Tuberculous and Other Nonsyphilitic Cases of Meningitis, Am. J. M. Sc. **178**:632, 1929.

quent in the literature. Pillotti [9] reported 1 case of tuberculous meningitis in a syphilitic patient who had had antisyphilitic treatment. Mallardi [10] presented a case with this combination, in which, judging from laboratory and clinical observations, it was difficult to decide exactly whether the child had a tuberculous or a syphilitic meningitis.

In our case, although tuberculosis of the meninges may have existed from the beginning, the evidence suggesting the presence of syphilitic meningitis at the onset is too strong to overlook. The fact that the patient improved under antisyphilitic treatment may also suggest the diagnosis of syphilitic involvement. It is possible and it is our belief that the iodides, which were given both intravenously and by mouth, may have been instrumental in the breaking down of a healed tuberculous focus either in the lungs or more likely in a lymph node. The tubercle bacilli thereby set free settled down on the already weakened meninges and this resulted in a more or less localized meningitis. The fact that the patient recovered need not exclude the diagnosis of tuberculous meningitis.

## CURABILITY OF TUBERCULOUS MENINGITIS

There have been many contributions in the literature pertaining to the curability of tuberculous meningitis. Rillet is credited with the first discussion in 1853. The number of patients reported as cured would probably mount to 400 or more. Cramer and Bickel collected 250 cases; others have similarly collected groups of reported cures, but when these reports are carefully scrutinized, the number of acceptable authentic cases is considerably less. Of the 250 cases collected by Cramer and Bickel, they considered only 46 as authentic; Martin, in 1909, collected 20 cases; Pitfield, in 1913, in his contribution raised the number to 29 cases; Harbitz,[11] in 1921, and Borrusso, in 1929, also gathered case reports in their discussions on the curability of tuberculous meningitis.

We have attempted to compile a complete list of the reported cures and have arranged them in tabular form. In this way, repetition and unintentional exaggeration of the figures were obviated. In selecting authentic cases, the qualifications already mentioned in the discussion of the diagnosis of our case were adhered to. We included Schaeffer's [12]

9. Pillotti, quoted by Schaffle and Riesenberg: Am. J. M. Sc. **178**:633, 1929.

10. Mallardi, M.: Un caso di meningite sifilitica in soggeto tubercolotico, Pediatria **28**:1138, 1920.

11. Harbitz, F.: The Curability of Tuberculous Meningitis, Am. J. M. Sc. **161**:212, 1921.

12. Schaeffer, S.: Tuberculous Meningitis: Report of a Case in an Adult, with Recovery, New York M. J. **48**:77, 1913.

case because of the positive results after inoculation into a guinea-pig. Additional cases recently reported are those of Gehrke,[13] Vialard and Darleguy,[14] Vedel, Giraud and Puesch,[15] McMahon,[16] Neidhardt,[17] Oppenheim,[18] Wiese,[19] Dima [20] and Jousset and Perisson.[21] These cases, together with ours, raised the number to 73. Reports of cures without sufficient scientific proof of the diagnosis were discarded.

It may be pertinent to take up the question as to what constitutes a cure. Some patients who were reported as cured had recurrences of meningitis, and in isolated cases the recurrences were fatal. This question cannot be settled definitely as there are no iron-clad rules to follow in deciding the point. An arbitrary period of freedom from symptoms and subsidence of the infection may be designated. Since tuberculous meningitis is considered a fatal disease, may it not be assumed that if the patient has recovered from the symptoms and signs sufficiently to get about, leave the hospital and remain free from the symptoms for from six to twelve months, his case may be classified as a "cure." A "cure" in a case of tuberculous meningitis should really be interpreted as a clinical recovery through which the patient has escaped an apparently inevitable doom that awaits sufferers of this disease. The patients who have recovered may show some after-effects or sequelae in various forms. However, the fact remains that the patients did not die, and hence they are referred to as being "cured" or having "recovered."

Table 2 shows the statistical data of the cases reported as cures and the authors who quoted them.

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13. Gehrke, A.: Kann die Meningitis tuberculosa Heilen? Beitr. z. Klin. d. Tuberk. **61**:310, 1925.

14. Vialard and Darleguy: Recovery from Tuberculous Meningitis, Bull. et mém. Soc. méd. d. hôp. de Paris **49**:522, 1925.

15. Vedel; Giraud, and Puesch: Acute Tuberculous Meningitis, Bacteriologically Confirmed, Rapid Recovery Persisting for Thirty-Two Months, Bull. et mém. Soc. méd. d. hôp de Paris **50**:388, 1926.

16. McMahon, B. T.: Recovery from Tuberculous Meningitis, Am. Rev. Tuberc. **13**:216, 1926.

17. Neidhardt, K.: Recovery of Case of Tuberculous Meningitis After Intra-Lumbar Treatment with Tuberculin, München. med. Wchnschr. **73**:823, 1926.

18. Oppenheim, E. A.: Tuberculous Meningitis Cured by Freedman Vaccination, Ztschr. f. Tuberk. **45**:316, 1926.

19. Wiese, O.: Recovery from Tuberculous Meningitis, München. med. Wchnschr. **73**:1937, 1926.

20. Dima, F.: Apparent Cure of Tuberculous Meningitis and Recurrence, Riforma med. **45**:990, 1929.

21. Jousset, A., and Perisson, J.: Cure of Tuberculous Meningitis or Remission in Three Cases Treated with Allergine (Tuberculous Vaccine), Bull. et mém. Soc. méd. d. hôp. de Paris **53**:654, 1929; Rev. internat. de méd. et de chir. **40**:75, 1929.

It is almost impossible to collect all of the cases of tuberculous meningitis terminating favorably. No one can say how many cases were rejected because of insufficient scientific data, e. g., Browning's [22] 4 cases and others, may actually have been infections due to the tubercle bacillus. This applies to patients in whose cases the clinical evidence pointed to tuberculous meningitis but in which proper laboratory studies were not carried out. In the cases reported by Hamill [23] and the one quoted by Abt,[24] the diagnosis was acceptable, but the reports were never included in the literature because of the aforementioned reasons. On the other hand, there may have been genuine cases of tuberculous meningitis terminating in recovery, but on account of the rarity of the condition the physicians hesitated to diagnose them as such and considered Koch's infection as the etiologic factor. However, even with the limited number of cases available, one must admit that some cases may be exceptions to the general rule and that patients do recover from this disease.

An analysis of the 73 cases reveals the following statistics as to sex, age and laboratory observations:

| | Number of Cases | Percentage |
|---|---|---|
| Males | 40 | 55 |
| Females | 23 | 31 |
| No mention of sex | 10 | |

| | Cramer and Bickel's List of 46 Cases | | Author's List of 73 Cases, Including Cramer and Bickel's | |
|---|---|---|---|---|
| Age, Years | Number of Cases | Percentage | Number of Cases | Percentage |
| Up to 2½ | 1 | 2.5 | 1 | 1.4 |
| 2½ to 5 | 6 | 15.0 | 14 | 19.2 |
| 6 to 10 | 10 | 25.0 | 12 | 16.4 |
| 11 to 20 | 11 | 27.5 | 14 | 19.2 |
| Above 20 | 12 | 30.0 | 24 | 33.0 |
| Not mentioned | 6 | .... | 8 | .... |

## SIGNIFICANCE OF LABORATORY STUDIES

The tubercle bacillus was present in the spinal fluid in 47 cases (64 per cent); it was not found in 16 cases (22 per cent), and it was not mentioned in 10. When the spinal fluid was inoculated into a guinea-pig, tuberculosis resulted in 30 instances (41 per cent); the inoculation was negative in 4 cases (6 per cent) and was either not done or at least not mentioned in 39 cases (53 per cent). This procedure evidently has been neglected in many cases, and in view of the importance of definitely establishing a diagnosis, it may be worth while to emphasize that nothing should be omitted when laboratory studies are

22. Browning, C. C.: Report of Four Cases of What Appeared to Be Tuberculous Meningitis with Apparent Permanent Arrestment, Med. Rec. **86**:325, 1914.

23. Hamill: Tr. Am. Pediat. Soc., Arch. Pediat. **27**:697, 1910.

24. Abt: Tr. Am. Pediat. Soc., Arch. Pediat. **27**:698, 1910.

TABLE 2.—*Analysis of Authentic Cases of Tuberculous Meningitis Terminating in Recovery*

| Report of Case | | Quoted by | Sex | Age, Years | Duration of Illness | Site of Tubercle Bacilli | Tubercle Bacilli in Choroid | Tubercle Bacilli in Spinal Fluid | Guinea-Pig Inoculation | Cytodiagnosis | Autopsy | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Rillet..... | 1853 | Harbitz | .. | 5½ | 3 months | ..... | ..... | ..... | ..... | ..... | Confirmed | |
| 2. von Bokai... | 1862 | Harbitz | F | 4 | ..... | Lung | ..... | ..... | ..... | ..... | Confirmed | |
| 3. von Leube... | 1889 | Harbitz | .. | .. | ..... | ..... | ..... | ..... | ..... | ..... | Confirmed | |
| 4. Barth..... | 1894 | Harbitz | M | 12 | ..... | ..... | ..... | ..... | ..... | ..... | Confirmed | |
| 5. Freyhan..... | 1894 | Cramer and Bickel | M | 20 | 3 months | ..... | ..... | Positive | ..... | ..... | ..... | Well 5 months later |
| 6. Janssen..... | 1896 | Harbitz | M | 19 | 6 weeks | Lung | ..... | Positive | ..... | ..... | Confirmed | Died 3 years later of tuberculosis of lung |
| 7. Busse..... | 1896 | Harbitz | F | 37 | 8 months | ..... | ..... | Positive | ..... | ..... | ..... | |
| 8. Henkel..... | 1900 | Cramer and Bickel | M | 10 | ..... | ..... | ..... | Positive | ..... | ..... | ..... | Complete cure |
| 9. Rocaz..... | 1901 | Martin | M | 8 | 9 months | Lung | ..... | ..... | ..... | Lymphocytosis | Confirmed | Recurrence 22 months later |
| 10. Barth..... | 1902 | Cramer and Bickel | F | 2¾ | 6 months | ..... | ..... | Positive | ..... | ..... | ..... | Complete cure |
| 11. Gross..... | 1902 | Cramer and Bickel | F | 17 | Short | Glands and lungs (?) | ..... | Positive | ..... | Polymorphonuclear | ..... | |
| 12. Alanzino.... | 1903 | Cramer and Bickel | .. | .. | ..... | ..... | ..... | Negative | Positive | Lymphocytosis | ..... | Well 3 months later |
| 13. Rossini..... | 1905 | Martin | .. | .. | ..... | ..... | ..... | ..... | Positive | ..... | ..... | Complete recovery |
| 14. Carriere and L'Hote | 1905 | Cramer and Bickel | M | 5 | Short | ..... | ..... | Negative | Positive | Lymphocytosis | ..... | |
| 15. Carriere and L'Hote | 1905 | Cramer and Bickel | M | 7 | ..... | Glands | ..... | Negative | Positive | Lymphocytosis | ..... | |
| 16. Carriere and L'Hote | 1905 | Cramer and Bickel | M | 6½ | 2 months | Glands | ..... | Positive | Postive | Lymphocytosis | ..... | |
| 17. Carriere and L'Hote | 1905 | Cramer and Bickel | F | 4 | ..... | ..... | Positive | Negative | Positive | Lymphocytosis | ..... | |
| 18. Sicard..... | 1905 | Cramer and Bickel | M | 33 | 5 weeks | ..... | ..... | ..... | Positive | Lymphocytosis | Confirmed | Recurrence 3 months later; fatal recurrence in 4 years |
| 19. Glaisse and Abrami | 1905 | Cramer and Bickel | M | 30 | 3 months | ..... | ..... | Positive | Positive | Lymphocytosis | ..... | Complete cure |
| 20. Vaquez and Digne | 1905 | Cramer and Bickel | M | 25 | 5 weeks | ..... | ..... | Negative | Positive | ..... | ..... | |
| 21. Tedeshi..... | 1905 | Cramer and Bickel | F | 14 | ..... | ..... | ..... | Negative | Positive | Lymphocytosis | ..... | Well 7 months later |
| 22. Riebold..... | 1906 | Cramer and Bickel | F | 6 | 2 months | ..... | ..... | Positive | Positive | ..... | ..... | Well 6 months later |
| 23. Hutinel and Tixier | 1907 | Cramer and Bickel | M | 5 | 5 weeks | Glands | ..... | ..... | Positive | ..... | ..... | Well 7 months later |
| 24. Jemma..... | 1907 | Cramer and Bickel | M | 3½ | Slow cure | ..... | ..... | Negative | Positive | Lymphocytosis | Confirmed | Confirmed after 3 years |
| 25. Rumpel..... | 1907 | Cramer and Bickel | M | 9 | Extremely slow, 3 months | Lungs 4 years later | ..... | Positive | ..... | ..... | 8 years, confirmed | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 26. Garelso..... | 1908 | Cramer and Bickel | M | 8 | ..... | ..... | ..... | Negative | Positive | Lymphocytosis | ..... | Complete cure 2 years later |
| 27. Stark..... | 1908 | Cramer and Bickel | M | 44 | ..... | ..... | ..... | Positive | ..... | ..... | ..... | Complete cure |
| 28. Stiles..... | 1908 | Cramer and Bickel | .. | .. | ..... | ..... | ..... | Positive | ..... | ..... | ..... | |
| 29. Stiles..... | 1908 | Cramer and | .. | .. | ..... | ..... | ..... | Positive | ..... | ..... | ..... | Cure with right hemiplegia |
| 30. Dunn..... | 1910 | Dunn | F | 3 | 3 weeks | ..... | ..... | Positive | ..... | ..... | ..... | |
| 31. Warrington | 1910 | Cramer and Bickel | M | 11 | Slow cure, several months | ..... | ..... | Positive | ..... | ..... | ..... | |
| 32. Castaigne and Gouraud | 1911 | Cramer and Bickel | M | 20 | ..... | ..... | ..... | Positive | Positive | ..... | ..... | Cure confirmed 1 year later |
| 33. Aviragnet and Tixier | 1911 | Cramer and Bickel | M | 5 | 5 weeks | Glands | ..... | Negative | Positive | ..... | ..... | Well 7 months later |
| 34. Archangelsky | 1911 | Cramer and Bickel | F | 8 | ..... | ..... | ..... | Positive | Negative | ..... | ..... | Well 2 years later |
| 35. Wanietschek | 1911 | Cramer and Bickel | M | 4 | 6 weeks | ..... | ..... | Positive | ..... | ..... | ..... | |
| 36. Hockstetter | 1912 | Cramer and Bickel | M | 21 | Slow cure, 6 months | Lung, right apex | ..... | Positive | Negative | ..... | ..... | |
| 37. Barbier and Gougelet | 1912 | Cramer and Bickel | M | 5 | ..... | Lung | ..... | Negative | Positive | ..... | ..... | Well 1 year; fatal recurrence |
| 38. Mlle. Cottin | 1912 | Cramer and Bickel | M | 21 | 2½ months | Lung | ..... | Positive | Positive | ..... | ..... | Well 8 months later |
| 39. Brooks, Tyrrel and Gibson | 1912 | Cramer and Bickel | F | 4 | ..... | Lungs (later) | ..... | Positive | ..... | ..... | Confirmed | Died several years later of tuberculosis |
| 40. Schaeffer.... | 1913 | Kramer and Stein | M | 39 | 2-3 weeks | ..... | ..... | Negative | Positive | Polymorphonuclears | ..... | |
| 41. Reichman and Ranch | 1913 | Cramer and Bickel | F | 21 | ..... | Pleurisy | ..... | Positive | Negative | ..... | ..... | Complete cure |
| 42. Bezancon and Gastonel | 1913 | Cramer and Bickel | .. | .. | 2 months | ..... | ..... | Negative | Positive | ..... | ..... | Complete cure |
| 43. Pitfield..... | 1913 | Cramer and Bickel | M | 55 | 3 weeks | Chronic pulmonary involvement | ..... | Positive | ..... | ..... | ..... | Well 2 years later |
| 44. Estramann.. | 1914 | Harbitz | M | 37 | 1 year | Lymph nodes and skin | ..... | Positive | ..... | ..... | Confirmed | |
| 45. Rossle..... | 1914 | Harbitz | F | 37 | 17 months | Tracheal lymph nodes | Positive | Negative | ..... | ..... | Confirmed | |
| 46. Bokay..... | 1914 | Cramer and Bickel | M | 11 | ..... | Abdomen | ..... | Negative | Positive | ..... | ..... | Well 1 year later |
| 47. Bokay..... | 1914 | Cramer and Bickel | M | 12 | ..... | ..... | ..... | Positive | Positive | ..... | ..... | Well 2½ years later |
| 48. Fonzo..... | 1915 | Cramer and Bickel | .. | 11 | ..... | ..... | ..... | Positive | ..... | ..... | ..... | Complete cure |
| 49. Bacigalupo.. | 1915 | Cramer and Bickel | .. | .. | 20 days | ..... | ..... | Positive | ..... | ..... | ..... | Complete cure |
| 50. Bacigalupo.. | 1915 | Cramer and Bickel | .. | .. | 20 days | ..... | ..... | Positive | ..... | ..... | ..... | Complete cure |
| 51. Tilli..... | 1916 | Cramer and Bickel | F | 7 mo. | 2 months | ..... | ..... | Positive | Positive 30 months later | ..... | ..... | Fatal recurrence 6 months later |

TABLE 2.—*Analysis of Authentic Cases of Tuberculous Meningitis Terminating in Recovery—Continued*

| Report of Case | | Quoted by | Sex | Age, Years | Duration of Illness | Site of Tubercle Bacilli | Tubercle Bacilli in Choroid | Tubercle Bacilli in Spinal Fluid | Guinea-Pig Inoculation | Cytodiagnosis | Autopsy | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 52. Tilli..... | 1916 | Cramer and Bickel | M | 8 | ..... | ..... | ..... | Positive | ..... | ..... | ..... | Recurrence in 2 months, cure with sequelae |
| 53. Grote..... | 1917 | Cramer and Bickel | F | 27 | 2 months | ..... | ..... | Positive | ..... | ..... | ..... | |
| 54. Grote..... | 1917 | Cramer and Bickel | F | 12 | 1 month | ..... | ..... | Positive | ..... | ..... | ..... | |
| 55. Van den Bogert | 1918 | Cramer and Bickel | F | 3½ | 6 months | ..... | ..... | Negative | Positive | ..... | ..... | |
| 56. Harbitz..... | 1919 | Harbitz | M | 32 | ..... | ..... | ..... | Positive | ..... | ..... | ..... | |
| 57. Harbitz..... | 1919 | Harbitz | M | 30 | 4 months | ..... | ..... | Positive, after death | ..... | ..... | ..... | |
| 58. DeMassary.. | 1920 | Cramer and Bickel | F | 23 | ..... | Pulmonary infection suspected | ..... | Positive | ..... | ..... | ..... | Complete cure |
| 59. Barber and L'Echelle | 1920 | Cramer and Bickel | F | 37 | Chronic course 6 months | Fibroid | ..... | Positive | ..... | ..... | ..... | Complete cure |
| 60. Cramer and Bickel | .... | Cramer and Bickel | M | 19 | 2½ months | Lungs (?) | ..... | Negative | Positive | ..... | ..... | Complete cure 18 months later |
| 61. Gehrcke..... | 1925 | Kramer and Stein | F | 33 | 7 months | Lungs | ..... | Positive | Positive | ..... | ..... | Hemiplegia |
| 62. Vialard and Darleguy | 1925 | Kramer and Stein | M | 22 | 5 months | ..... | ..... | Positive | Positive | Lymphocytosis | ..... | Well 6 months later |
| 63. Vedel, Giraud and Puesch | 1926 | Kramer and Stein | F | 23 | 1 week | ..... | ..... | Positive | Positive | Lymphocytosis | ..... | Well 32 months later |
| 64. McMahon... | 1926 | Kramer and Stein | F | 28 | 1 year | Lungs | ..... | ..... | Positive | Lymphocytosis | ..... | Well 10 months later |
| 65. Neidhardt... | 1926 | Kramer and Stein | M | 12 | 3 weeks | ..... | ..... | Positive | ..... | Lymphocytosis | ..... | |
| 66. Oppenheim.. | 1926 | Kramer and Stein | M | 10 | 14 days | Lungs | ..... | Positive | ..... | ..... | ..... | Well some months later |
| 67. Wiese..... | 1926 | Kramer and Stein | M | 10 | 5 months | ..... | ..... | Positive | ..... | Lymphocytosis | ..... | Recovery |
| 68. Dima..... | 1929 | Kramer and Stein | M | 4 | 7 weeks | ..... | ..... | Positive | ..... | Lymphocytosis | ..... | Recurrence |
| 69. Borruso..... | 1929 | Kramer and Stein | M | 3½ | 12 days | Knee (5 mo. later) | ..... | ..... | Positive | Lymphocytosis | ..... | Recovery |
| 70. Jousset and Perisson | 1929 | Kramer and Stein | F | 31 | 6 months | ..... | ..... | Positive | ..... | Lymphocytosis | ..... | Well 6 months later |
| 71. Jousset and Perisson | 1929 | Kramer and Stein | F | 18 | 2 months | ..... | ..... | Positive | ..... | Polymorphonuclears | ..... | Four months later, sick 2 weeks; final recovery |
| 72. Jousset and Perisson | 1929 | Kramer and Stein | M | 36 | 2 months | ..... | ..... | Positive | ..... | Lymphocytosis | ..... | Apparently well 7 months later |
| 73. Kramer and Stein | | | M | 29 | 10 days | Lungs; glands | ..... | Positive | Negative | Lymphocytosis | ..... | Well 2 years later |

carried out in suspected cases of meningitis. In 15 cases in which the tubercle bacilli could not be demonstrated in the spinal fluid, the diagnosis was established by positive inoculation into guinea-pigs. This fact is important because in some cases the organisms are so few as to make it exceedingly difficult to demonstrate their presence under the microscope. The doubly positive observation in which tubercle bacilli were present in the spinal fluid with positive inoculation into a guinea-pig was found in only 10 cases (13.7 per cent) of the series.

Cytodiagnosis was mentioned in 24 of the cases. Lymphocytosis was the usual observation; however, on three occasions polymorphonuclears predominated.

Tuberculous lesions elsewhere in the body may be of interest when discussing the possible explanations for recovery in tuberculous meningitis. This condition was present in twenty-six patients (35.6 per cent). The most common site was in the lungs and the pleura (18 cases); the lymph glands were next (7 cases), and there was one instance each of infection in the abdomen, the knee and the skin.

## EXPLANATION OF RECOVERY IN TUBERCULOUS MENINGITIS

The possible reasons for favorable termination of this most dreaded disease may be grouped under three headings: (*a*) clinical, (*b*) bacteriologic and (*c*) pathologic. Under the first group, age is important. A glance at the tabulation containing the incidence according to age shows that up to 2½ years only one patient recovered. Except for the discrepancy in the period from 2½ to 5 years, one could well infer that the older the patient, the better his chances for escaping the almost inevitable fatal termination. This deduction was well demonstrated in Cramer and Bickel's table. No doubt, advancing age does give the person more powers of resistance. One need merely mention the unusually high mortality rate for tuberculous meningitis in infants. The disease is invariably fatal up to 2 years. Besides the natural resistance that develops with years, it is also possible that the tissues gradually learn to cope with the tubercle bacilli. This has been mentioned by some authors who look on healed lesions in the lungs or old glandular infections as having the same beneficial effect as a vaccine would have. It is possible that the tissues may develop some immunologic properties that enable the person to limit the infection and ultimately to control it.

Bacteriologic influences depend on the number of organisms, their virulence and also the strain. It is possible that the favorable termination in some of the cases may have been due to the small numbers of tubercle bacilli distributed throughout the body. This fact was also mentioned in the discussion of the unsuccessful inoculation of tubercle bacilli into guinea-pigs. Virulence of the organism and its rôle in infec-

tion are too well known. Discussion on this phase seems unnecessary. Another point of interest may be the influence of the type of organism or strain of tubercle bacilli on recovery. Cramer and Bickel [25] and Landouzy and Gougerot [26] discussed what may be considered a peculiar form of reaction of the tissues to the infection. They emphasized the fact that the usual tendency for the formation of tubercles was lacking in these cases. Pathologic reports on the appearance of these cases, which were studied at later times, mentioned the fact that the meninges were congested and infiltrated, with thickening. There may be abundant exudate, but no tubercles in the subarachnoid space. The tendency to fibrosis is apparent. The brain is only slightly involved. There is a lessened tendency to overdistention of the ventricles with fluid. This may be due to a diminished inflammatory reaction of the meninges and the brain. Microscopically, intense congestion of the meninges with infiltration was noted; there was no nodular formation; many bacilli were found in the sections and many in the fluid. The presence of tuberculous meningitis as part of a generalized tuberculosis is a hopeless situation.

### PROGNOSIS

The outlook for the patients who have survived is uncertain. Many cases have been observed for three years without a recurrence. However, some of them subsequently have reinfections, either in the form of a meningitis or the breaking down of another focus, which may terminate fatally. Some of the cases have sequelae in the form of deafness, monoplegia, blindness or persistent headaches.

We doubt whether much can be learned from a study of these cases with the hope of improving our therapeusis. Some physicians have been enthusiastic concerning their particular form of treatment, which varies from tuberculin therapy to surgical intervention. Decompression has been attempted; repeated lumbar punctures have been endorsed by some; autoserotherapy by reinoculation of the spinal fluid has been advised, and injections of tuberculin, both under the skin and into the dura, have been tried. It is questionable whether any form of treatment can be proved to be a determining factor in the recovery. It is possible that repeated spinal punctures may help to give relief and may spare some damage to the cerebral tissue from overdistention of the ventricles. It is likely that when a patient does recover the main factors are the individual resistance and a lowered virulence of the infecting agent.

The prognosis of tuberculous meningitis is still extremely doubtful. One cannot tell offhand which patients have a chance for recovery, but

25. Cramer and Bickel, p. 239 (footnote 4).

26. Landouzy and Gougerot, quoted by Borrusso, p. 499 (footnte 5).

we agree with Dunn [27] that the family may be encouraged with the fact that there is a possible chance for a favorable termination, however remote that chance may be. No rules can be formulated with the type of onset as a guide because among the recoveries reported, some cases appeared with explosive symptoms while others began with a mild onset. The older the patient, the greater is the resistance and the better is the chance for a favorable result.

## SUMMARY AND CONCLUSIONS

The report of a case in a Negro with evidences of syphilitic meningitis has been given; subsequent observations of tuberculous meningitis were made, and a favorable termination reported. A review of the literature reveals a number of contributions on the curability of tuberculous meningitis and numerous reports of cures. This number has been considerably reduced because of insufficient scientific data.

Seventy-three cases of presumably authentic cures were collected. A study of this group of cases does not enlighten us with information that may be of value in the direct treatment for this disease in the future.

Cures have been attributed to various factors such as the age and the resistance of the patient and a low virulence of the organism. Statistics of the collected cases show the highest percentage of cures among patients above 20 years of age (33 per cent) and the lowest percentage in infants.

The traditional and fixed idea that a patient with tuberculous meningitis must die should be reconsidered. No doubt, a recovery is extremely rare, but no one can foretell when this unexpected favorable termination may occur. The tendency to discard the diagnosis of tuberculous meningitis and disregard such laboratory observations as the presence of tubercle bacilli and successful inoculation into guinea-pigs, merely because the patient recovered, seems unscientific and illogical.

Dr. Walter J. Crocker and the laboratory staff gave excellent cooperation in managing the scientific studies in this case.

27. Dunn, C. H.: The Cytodiagnosis of Tuberculous Meningitis and the Possibility of Recovery, Arch. Pediat. **27**:685, 1910.

# THE CAUSE OF EXOPHTHALMIC GOITER

## A BIOCHEMICAL HYPOTHESIS *

WILLIAM S. REVENO, M.D.
DETROIT

It is quite generally agreed, although with some dissatisfaction, that the thyroid gland is responsible, when abnormally active, for the symptoms that characterize exophthalmic goiter. A vast literature has accumulated on this subject, with the majority of writers and investigators favoring the thyrogenic origin of the disease. A few have taken exception to this view; the most notable among these being McCarrison, who for many years has stoutly maintained that the disease is of toxic origin, and that the toxin or toxins originate in the intestinal tract. Plummer,[1] who favors the thyrogenic theory, described the disease as one in which the symptoms are due to dysfunction of the thyroid, excess thyroxine as well as an abnormal substance being present. McCarrison,[2] however, stated that "in the vast majority of cases the excitation which determines the gland's derangement is toxic, and is one which initiates disturbances of the whole endocrine system." There is an obvious difference of opinion in these two views, a difference that will not be adjusted until a more accurate knowledge is had of all of the disturbing substances other than thyroxine whether they originate in the thyroid or elsewhere. The view held by McCarrison seems to have the advantage in that it is arrived at by a consideration of the rôle played by three factors, nutritional, psychic and toxic. By his extensive studies of the changes produced in the thyroid gland in disturbances of nutrition and in toxic states, McCarrison established a strong support for his attitude. He showed in a convincing manner that changes that tend to destroy functioning thyroid tissue and ultimately to produce a condition of hypofunction may be induced by the toxins resulting from the feeding of infected material; also [3] that the ingestion of amino-acids has an effect on the thyroids of tadpoles—a reduction in the size and number of the vesicles, and a decrease in the weight and length of the gland resulting. Tyrosine is the only one of the amino-acids that sometimes causes congestive and degenerative changes. McCarrison investigated also the effects of ingestion of histamine and tyramine on pigeons and rats [4] and found a tendency for a reduction in

* Submitted for publication, Jan. 2, 1931.

1. Plummer, H. S., quoted by Kendall, E. C.: Thyroxine, Am. Chem. Soc. Monog. Ser. No. 47, New York, The Chemical Catalog Company, 1929.

2. McCarrison, R.: The Thyroid Gland, New York, William Wood & Company, 1917.

3. McCarrison, R.: Indian J. M. Research **11**:1136, 1924.

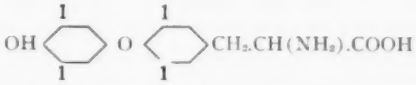
4. McCarrison, R.: Indian J. M. Research **11**:1154, 1924.

the size of the thyroid by both amines. He expressed the opinion that the ingestion of tyramine may possibly cause exophthalmos although this result may be rare. This evidence, while it may not be altogether convincing, serves a purpose in pointing an accusing finger at the intestinal tract as the source for the substances that are responsible for the disturbance known as exophthalmic goiter.

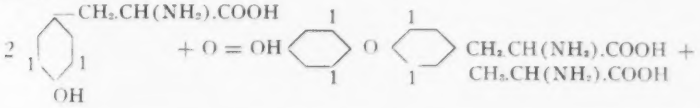
The symptoms in exophthalmic goiter may be adequately divided into those that are produced by thyroxine and those produced by a substance resembling epinephrine. From the present knowledge of the pharmacologic action of thyroxine, such symptoms as loss of weight, gastro-enteritis, diarrhea and tachycardia proportionate to the increase in metabolism may be readily explained. The symptoms attributable to the epinephrine-like substance do not, however, conform to the recognized major pharmacologic effects of epinephrine and it is necessary, therefore, to look to other substances, closely related to epinephrine, as being responsible for the extreme irritability of the vegetative nervous system, the tremor, elevated blood pressure and exophthalmos.

## CHEMICAL COMPOSITION OF THYROXINE, EPINEPHRINE AND TYRAMINE

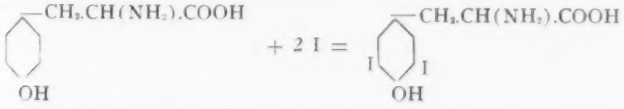
There is a most interesting connection between the chemical constitution of thyroxine and epinephrine. Thyroxine was isolated originally by Kendall in 1915,[5] and the chemical formula was determined as



by Harington and Barger,[6] who showed conclusively that it resulted from the oxidation of two molecules of 3:5 diiodotyrosine in this manner:



The 3:5 diiodotyrosine, which is the precursory substance of thyroxine, is derived from the amino-acid tyrosine by the addition of two atoms of iodine in the 3 and 5 positions in the benzene ring:



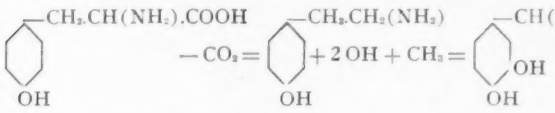
5. Kendall, E. C.: The Isolation in Crystalline Form of the Compound Containing Iodin, Which Occurs in the Thyroid, J. A. M. A. **64**:2042 (June 19) 1915.

6. Harington, C. R., and Barger, G.: Biochem. J. **21**:169, 1927.

According to Oswald,[7] diiodotyrosine may in turn be deiodized by trypsine in the alimentary canal.

The amino-acid tyrosine normally produced in the intestinal tract as an end-product of the digestion of protein is therefore the parent substance of thyroxine; 3:5 diiodotyrosine is also produced in the intestine since it has never been isolated in crystalline form from the thyroid gland (although it may be present there)[8] and, too, with both iodine and tyrosine present in the same region, it is fair to assume that synthesis of diiodotyrosine may logically take place there.

Epinephrine is 1,2 hydroxyphenyl, 4 hydroxyethlmethylamine, and is derived from tyrosine first by splitting off $CO_2$, forming hydroxyphenylethylamine, and then by oxidation and methylation to epinephrine:




It is probably produced in the intestine, and its content in excised suprarenal glands may be increased by incubation with tyrosine.[9]

There is a common source in tyrosine for both thyroxine and epinephrine, and the suggestion occurs at this point that disturbances in the normal metabolism of this amino-acid may constitute the underlying factor in exophthalmic goiter.

As far as is known, tyrosine is utilized for the production of two very important substances, thyroxine and epinephrine. Any excess probably undergoes decomposition by intestinal bacteria to phenol, p-cresol and p-hydroxyphenylacetic acid (by decarboxylization), and to tyramine. These substances are probably detoxicated by the liver, the phenols being eliminated as ethereal sulphates, and the tyramine as p-hydroxyphenylacetic acid.[10] Certain conditions may, however, interfere with this orderly procedure, and the overproduction of tyramine, a base in which the action resembles that of epinephrine in many respects, may result.

### CHANGES IN THE NORMAL TYROSINE-TYROSINASE REACTION

The first of these conditions is an alteration in the reaction between tyrosine and the ferment tyrosinase whereby the pigment melanin results. Under normal conditions, this reaction proceeds in the follow-

7. Oswald: Ztschr. f. physiol. Chem. **62**:432, 1909.
8. Kendall, E. C.: Thyroxine, Am. Chem. Soc. Monog. Ser. No. 47, New York, The Chemical Catalog Company, 1929.
9. Halle, W. L.: Beitr. z. chem. Phys. u. Path. **8**:276, 1906.
10. Stewart, F. H.: J. Ment. Sc. **75**:53, 1929.

ing manner:[11] Tyrosine and tyrosinase together form red pigment. (This is the pigment responsible for the red discoloration that appears on the cut surface of raw potato when exposed to the air). After several hours, this red substance becomes colorless; this phase of the reaction is accomplished best in a vacuum or in the presence of an inert gas in a medium ranging between $p_{H_6}$ and $p_{H_8}$. Finally, this colorless substance is converted to melanin in the presence of oxygen. Presumably, under altered conditions, such as an excess of tyrosine or a lack of tyrosinase or a change in the hydrogen ion concentration or the gaseous tension of the medium, the normal reaction does not take place and the base tyramine may be produced.

The most important factor in the production of tyramine is that which is responsible for interference with the normal decomposition of tyrosine by bacteria. The production of tyramine from tyrosine is assumed to take place in the same manner and under the same conditions as the production of histamine from histidine. Folin and Denis[12] found that certain B. coli in alkaline intestinal mediums promote the destruction of tyrosine by decarboxylization and the production of phenols which are detoxified by the liver and eliminated by the kidney. These same bacilli will, in an acid medium, produce the base tyramine. Hanke and Koessler[13] found in a large series of experiments that the amines (tyramine and histamine) were not produced in a medium that contained no carbohydrate and in which an acid reaction was not developed. They stated that the amines can be thought of as buffers to reaction, and that their production from amino-acids is a protective mechanism which is resorted to when the accumulation of hydrogen ions within the organism's protoplasm threatens to destroy its life. In addition, they showed that the production of histamine from histidine may be either appreciably slowed or stopped altogether by forcing B. coli to grow anaerobically.[14] Weyl[15] showed that the putrefactive organisms, under conditions prevailing in the intestine, i. e., in the absence of oxygen, produce large quantities of phenols from tyrosine.

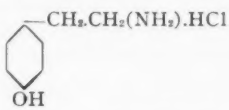
It is reasonable to assume that, with the presence of amino-acids other than tyrosine, under the altered conditions mentioned, amines other than tyramine, notably histamine, may be produced in the intestine. Histamine is antagonistic to tyramine in its action. It produces intense stimulation of tone and rhythm of the smooth muscles; it lowers the blood pressure by dilating capillaries[16] and because of its power as a

11. Raper, H. S., and Speakman, H. B.: Biochem. J. **20**:69 and 735, 1914.
12. Folin and Denis: J. Biol. Chem. **22**:309, 1915.
13. Hanke, M. T., and Koessler, K. K.: J. Biol. Chem. **59**:858, 1924.
14. Hanke and Koessler: J. Biol. Chem. **39**:581, 1919.
15. Weyl: Ztschr. f. physiol. Chem. **3**:312, 1879.
16. Sollmann, T.: A Manual of Pharmacology, Philadelphia, W. B. Saunders Company, 1927.

stimulant to smooth muscles, it may, in considerable amounts, produce diarrhea and vomiting.[17] The production of histamine along with tyramine is important because of the antagonistic action between these two agents. If it proceeds at a slow rate and in quantities sufficient for the effects of one to be neutralized by the effects of the other when both are absorbed, and if the rate of destruction is the same, then it may be assumed that few or no symptoms will result. If, however, there should be some disparity between the production, absorption or destruction of either of these bases, then it is conceivable that the resulting symptoms would depend on which of the bases was present in excess.

### THE PHARMACOLOGIC ACTION OF TYRAMINE

Tyramine, as has been mentioned, is a base in which the action resembles that of epinephrine. It is the hydrochloric acid salt of para-hydroxylphenylethylamine and is found in ergot. Its structural formula resembles that of tyrosine and epinephrine quite closely.




In action, according to Sollmann,[16] it is not as powerful as epinephrine, but is more persistent. It elevates the blood pressure, slowing the heart reflexly, and constricts the bronchioles. It sometimes stimulates gastric secretion (in cats only). Hewlett [18] reported that 20 mg. injected in man produces a rise in the systolic blood pressure, the diastolic being only slightly elevated, if at all. Subcutaneous injections in susceptible persons produce symptoms such as are found in exophthalmic goiter, namely: tremor, palpitation and anxiety. McCarrison [4] concluded, as a result of experiments on the effects of ingestion of tyramine and histamine in pigeons and rats, that tyramine may possibly produce exophthalmos.

How this powerful agent is detoxified is not altogether clear. Hare [19] expressed the belief that a definite enzymatic system is present in the liver for effecting rapid detoxication of excessive tyramine absorbed from the intestine by deamination and oxidation. This seems to offer a fairly logical explanation of the fate of this substance.

Tyramine, then, is a chemical agent that most probably plays an important part in the production of many of the symptoms in exophthalmic goiter. The responsibility for practically all of the symptoms

17. Mellanby, quoted by Alvarez, W. C.: Physiol. Rev. **4**:352, 1924.

18. Hewlett, A. W.: The Action of Tyramin, Arch. Int. Med. **21**:411 (March) 1918.

19. Hare, M. L. C.: Biochem. J. **22**:968, 1928.

in this disease may be placed on tyramine, epinephrine and thyroxine, all derived from the amino-acid tyrosine in abnormal quantities by an irregular metabolism.

SUMMARY

The hypothesis is advanced that exophthalmic goiter is primarily a disturbance resulting from a long-continued toxic process in the intestinal tract. This process not only damages the thyroid gland to the end that varying amounts of its functioning tissue are destroyed, but causes a faulty and irregular metabolism of the amino-acid tyrosine, so that an excess of thyroxine, epinephrine and tyramine is produced. These conclusions are reached in view of (1) the inadequacy of the thyrogenic theory of the disease; (2) the work of McCarrison on the effects of toxic material in the intestinal tract on the thyroid gland; (3) the close relationship between the chemical constitution of thyroxine epinephrine and tyramine, (4) the common source of these three substances, viz., tyrosine, (5) the changes in the normal tyrosine-tyrosinase reaction and the decarboxylization process for conversion of tyrosine to phenols, with resulting overproduction of the base tyramine, and (6) the pharmacologic action of tyramine.

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# THE ELIMINATION OF PHENOLSULPHONPHTHALEIN BY THE KIDNEY

## THE INFLUENCE OF PATHOLOGIC CHANGES IN THE LIVER *

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Many years ago when Rowntree and Geraghty [1] were investigating the elimination of phenolsulphonphthalein in abnormal renal conditions, it was observed that certain cases of intoxication in pregnancy showed an unusually high degree of elimination. It was suspected that these obstetric cases were complicated by some abnormality of the liver, which interested Dr. Whipple, who at that time was occupied with a study of experimental chloroform poisoning and hepatic injury.[2]

Subsequently, on several occasions in experiments dealing with experimental chloroform poisoning in dogs, it was observed that the renal elimination of phthalein was unusual. This applied to both phenolsulphonphthalein (renal function) and phenoltetrachlorphthalein (hepatic function [3]). Preliminary experiments recently (1926) carried out in this laboratory by Dr. D. J. Stephens and Dr. F. S. Hassett, were in accord with those tabulated in this paper. During the following year (1927), Dr. J. M. Scott and Dr. D. A. Weir completed a few observations of similar nature.

As it was obvious that hepatic injury modified the elimination of phenolsulphonphthalein by the normal kidney, we decided to study carefully the mechanism of this unexpected reaction. From the standpoint of interpretation of the elimination of phthalein by the normal or abnormal kidney, it would seem that a complete understanding of this phenomenon would be of value to the clinician who must evaluate the figures for phthalein in terms of renal dysfunction.

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* From the Department of Pathology, the University of Rochester School of Medicine and Dentistry.

1. Rowntree, L. G., and Geraghty, J. T.: J. Pharmacol. & Exper. Therap. **1**:579, 1909.

2. Whipple, G. H., and Sperry, J. A.: Bull. Johns Hopkins Hosp. **20**:278, 1909.

3. Whipple, G. H.; Peightal, T. C., and Clark, A. H.: Bull. Johns Hopkins Hosp. **24**:343, 1913.

It was first shown by Rowntree and Geraghty [4] that the liver was capable of excreting phenolsulphonphthalein. The dye appeared in the bile within an hour after the intravenous injection of 1 Gm. of phenolsulphonphthalein. Since only the faintest traces of phthalein could be found in the stools of animals, they concluded that a portion excreted in the bile is reabsorbed by the intestines and excreted by the kidneys.

While attempting to discover the fate of phthalein injected into animals, Kendall [4] found that when he mixed the dye with ground body tissue in vitro, after some hours it was partially reduced to a colorless substance. This occurred to the greatest extent when oxygen was eliminated from the mixture and when the liver, rather than the other organs, was used. He concluded that the liver is capable of destroying phthalein. Braasch and Kendall [5] stated that phenolsulphonphthalein may be destroyed by mixing it with body tissues in vitro when oxygen is absent, but for this to occur in life, such a degree of anoxemia must be present that death is impending. They showed that alkalosis tended to increase the urinary output of phenolsulphonphthalein, whereas acidosis decreased it. Marshall and Vickers [6] were able to recover 16 per cent of phenolsulphonphthalein from the liver of dogs killed fifteen minutes after 180 mg. of the dye had been injected, thus showing a marked affinity of the liver for phthalein.

After observing marked variations in the urinary output of phenolsulphonphthalein in normal persons, Major [7] investigated further the rôle of the liver in the destruction and retention of this dye. In rabbits he found a fairly uniform excretion, whether the phthalein was injected subcutaneously, intravenously or intrapleurally. However, when it was injected into the substance of the liver, a great reduction in the amount excreted in the urine occurred. When the dye was introduced into the portal vein, the amount eliminated in the urine was much less than when it was injected into the vena cava.

Möller and Lundsgaard [8] expressed the belief that the liver plays a part in the elimination of phthalein. They recovered from 1 to 3 per cent of the dye from the duodenal contents of three normal persons and none from five persons with hepatic disease. They investigated the fate of the dye excreted by the liver, and found that when phthalein was given by stomach tube only from 1 to 8 per cent could be recovered

4. Kendall, E. C.: Phenolsulphonphthalein, J. A. M. A. **68**:343 (Feb. 3) 1917.

5. Braasch, W. F., and Kendall, E. C.: J. Urol. **5**:127, 1921.

6. Marshall, E. K., Jr., and Vickers, J. L.: Bull. Johns Hopkins Hosp. **34**:1, 1923.

7. Major, R. H.: The Influence of the Liver on Phenolsulphonphthalein Excretion, J. A. M. A. **81**:1362 (Oct. 20) 1923.

8. Möller, E., and Lundsgaard, C.: Acta med. Scandinav. **63**:277, 1926.

in the urine and, as a rule, only a trace in the stools. They also found that the contents of the stomach in vitro did not destroy phthalein, whereas the feces did. In a series of patients with hepatic disease, these investigators [9] found that the elimination of phenolsulphonphthalein by the kidneys was prolonged and decreased. However, Chabanier and Gaume [10] stated that these patients showed evidence of renal insufficiency as well as hepatic disease. This would perhaps explain why the excretion of phenolsulphonphthalein was decreased rather than increased as one would be led to expect.

In a series of cases of obstructive jaundice without complicating renal disease, Abramson [11] did not note either a decrease or an increase in the output of phenolsulphonphthalein.

Recently, while our experiments were in progress, those carried out by Bernheim [12] and Olivet and Prüfer [13] and summarized by Schlayer,[14] in which the distribution of phthalein in the various tissues of the body was studied, came to our attention. They showed that thirty minutes after injection, the blood was practically free from phthalein; the dye was recovered subsequently in the various tissues of the body. Olivet and Prüfer found that the tissues of the kidneys, liver and skin showed the most marked affinity for phthalein. Traces of dye were found elsewhere, except in the brain and spinal fluid. In a pregnant dog none was found in the placenta nor in the amniotic fluid. They expressed the belief that as phthalein is excreted, the tissues gradually give up their store, and eventually most of the dye is excreted, the chief routes being the urine and the bile. They suggested that perhaps small amounts may be excreted by the skin, but this was not investigated. Their work led them to believe that from 20 to 30 per cent of the dye is excreted by the liver, and that the greater part of this is reabsorbed from the intestines, although when the dye was given by stomach tube, they could recover only small amounts in the urine. In a case of cirrhosis, they recovered from the urine 80 per cent of the amount of dye injected after one hour, and found that none could be regained from the duodenal contents. Olivet [15] recovered 90 per cent of the phthalein injected after two hours and 99 per cent after four hours from a dog in which the ductus choledochus had been tied for twenty-four hours. At autopsy, an extract of the

9. Möller, E., and Lundsgaard, C.: Acta med. Scandinav. **63**:268, 1926.
10. Chabanier, H., and Gaume, P.: Bull. Soc. franç. d'urol. **6**:69, 1927.
11. Abrahamson, H. A.: Excretion of Phenolsulphonphthalein in Obstructive Jaundice, Arch. Int. Med. **37**:291 (Feb.) 1926.
12. Bernheim, E.: Ztschr. f. klin. Med. **104**:240, 1926.
13. Olivet, J., and Prüfer, J.: Ztschr. f. klin. Med. **108**:653, 1928.
14. Schlayer, Carl R.: Ztschr. f. Urol. **23**:621, 1929.
15. Olivet, J.: Ztschr. f. klin. Med. **108**:665, 1928.

organs did not contain dye. They concluded that if the excretory and storing functions of the liver are blocked, the kidneys compensate and are able to excrete larger amounts of the dye. Tada[16] pointed out that in the case of dyes excreted by both the kidneys and the liver, if one path of excretion is impaired, the other compensates and excretes more than its normal amount. This seems to be true for phenolsulphonphthalein when excretion by the liver is impaired.

## METHODS

The general methods utilized were similar to those used by other investigators in this field. The solution of phthalein was made up as originally described by Rowntree and Geraghty so that 1 cc. contained 6 mg. of phenolsulphonphthalein. Only healthy, active, female dogs were used. In all instances the phthalein was injected into the jugular vein. Before each injection the bladder was emptied by catheter, and this urine was examined for albumin and microscopically for evidence of renal disease. Only dogs without evidence of renal disease were used. Unless otherwise noted, only 1 cc. of phenolsulphonphthalein was injected. This was measured with a 1 cc. pipet into a small dish. The pipet was then rinsed with physiologic solution of sodium chloride until no trace of the phthalein remained. The whole solution was then drawn up in a 10 cc. syringe. After the injection of phenolsulphonphthalein, the dogs were given 500 cc. of tap water by gavage in order to assure a fairly uniform and copious flow of urine. The urine was collected after one and two hours by means of a catheter, and the bladder was washed with 60 cc. of warm tap water after each catheterization in order to obtain all traces of phenolsulphonphthalein in the bladder. As a rule, the urine was not collected later than two hours after the administration of dye, since after this time only small amounts are excreted, and because this is the time limit usually followed in clinical studies.

The collected urine was made alkaline with sodium hydroxide and diluted with distilled water to 1,000 cc. after the first hour and to 500 cc. after the second. This solution was then filtered and read in a Dubocq colorimeter against a standard containing 3 mg. of phthalein per thousand cubic centimeters. The standard was freshly made twice a week. As a rule, no difficulty was experienced in matching the colors. When this happened, urine was added to the standard until a match could be obtained, the dilution being taken into account when the calculations were made.

In the dogs in which the common ducts were tied and the urine was highly colored with bile, we used the following method for precipitating the bile pigment: The urine was made alkaline by the addition of concentrated ammonia, and to each 50 cc. of urine, 10 cc. of a 10 per cent solution of calcium chloride was added. This was then centrifugated, and the clear supernatant fluid containing the phenolsulphonphthalein poured off. The precipitate was repeatedly washed with distilled water and centrifugated until the pink color could not be detected in the supernatant fluid. These washings were added to the original sample, diluted and compared in the usual way. As a rule, comparison with the standard was good. As a control, when phenolsulphonphthalein was added to varying amounts of urine and bile and treated as has been described we found that from 85 to 100 per cent of the dye could be recovered. The error increased with the amounts of urine and bile added.

16. Tada, Y.: Acta scholae med. univ. imp., Kioto **11**:243 and 253, 1928.

The same procedure was followed in the case of bile containing phenolsulphonphthalein. Each 10 cc. of bile was diluted to 50 cc. with distilled water, and made alkaline with concentrated ammonia. To this we added 10 cc. of the solution of calcium chloride. This was centrifugated, washed and diluted as described for the urine. Here, however, the matches in color were not quite as good. In control experiments in which from 10 to 30 cc. of bile was added to 3 mg. of phenolsulphonphthalein, we found that we were able to recover from 85 to 95 per cent of the dye by this method.

To produce chloroform poisoning, the dogs were starved for from twenty-four to sixty-four hours. A light surgical anesthesia was produced for from sixty to ninety minutes with chloroform. Following this, they did not receive food for twenty-four hours. An indication of the degree of hepatic damage was obtained by the determination of fibrin in some instances and by the icterus index in others.

The production of satisfactory damage to the liver by the administration of phosphorus was found to be difficult, because of the variations occurring in the reactions of the dogs to the solution used. The results of these experiments are inconclusive though in several instances suggestive. Stick phosphorus was dissolved in olive oil, 1 cc.: 10 mg. This was injected subcutaneously or intramuscularly.

## EXPERIMENTAL OBSERVATIONS

We shall cite only a few experiments which illustrate characteristic reactions to chloroform poisoning. We have on record a large number of similar experiments, and believe that the reactions tabulated here adequately show the character of the reaction and are fair examples of a considerable series.

As one might expect, the higher figures were observed in the more severe cases of hepatic injury due to chloroform and they persisted longer than in the cases of mild poisoning.

Table 1 shows the usual reaction to chloroform poisoning with a rise of from 10 to 15 points in the figures for the elimination of phthalein in the urine. The figures for fibrin prove beyond a doubt [17] that a fairly severe hepatic injury was produced by sixty minutes of chloroform anesthesia. It is well known [17] that within a few days the liver promptly repairs this type of injury, and that the blood fibrin then returns to normal. There is always a rise in the icterus index (table 2). In this experiment (table 1), the high values for the elimination of phthalein lasted four days and then fell toward normal.

As a control for the experiments on hepatic injury due to chloroform poisoning, we recorded the negative reaction to long periods of ether anesthesia preceded by fasting.

On the four days following the second experiment with chloroform anesthesia on the same dog (table 1), there were identical reactions and high figures for the elimination of phthalein. In spite of a longer fast and a somewhat longer duration of the anesthesia, the injury

17. Foster, D. P., and Whipple, G. H.: Am. J. Physiol. **58**:407, 1922.

TABLE 1.—*Severe Hepatic Injury and the Elimination of Phthalein in the Urine of Dog 29-32; Weight, 18.5 Kg.*

| Date | Output of Phenolsulphonphthalein, per Cent | | | Output of Urine, Cc. | | | Fibrin, Mg. per 100 Cc. |
|---|---|---|---|---|---|---|---|
| | First Hour | Second Hour | Total 2 Hours | First Hour | Second Hour | Total 2 Hours | |
| 11/19 | 75 | 9 | 84 | 35 | 124 | 159 | ... |
| 11/22 | 66 | 11 | 77 | 20 | 30 | 50 | ... |
| 11/23 | 65 | 7 | 72 | 30 | 51 | 81 | 264 |
| 11/25 | Chloroform anesthesia, 60 minutes; fasting, 24 hours | | | | | | |
| 11/26 | 84 | 11 | 95 | 30 | 121 | 151 | 221 |
| 11/27 | 82 | 11 | 93 | 57 | 170 | 227 | 76 |
| 11/29 | 86 | 10 | 96 | 150 | 200 | 350 | 125 |
| 11/30 | 80 | 6 | 86 | 38 | 105 | 143 | 202 |
| 12/ 2 | 69 | 11 | 80 | 95 | 160 | 255 | ... |
| 12/ 3 | 71 | 10 | 81 | 95 | 233 | 328 | ... |
| 12/ 7 | 69 | 8 | 77 | 95 | 205 | 300 | ... |
| 12/17 | 64 | 16 | 80 | 10 | 25 | 35 | ... |
| 12/20 | Ether anesthesia, 60 minutes; fasting, 24 hours | | | | | | |
| 12/22 | 72 | 8 | 80 | 60 | 300 | 360 | ... |
| 12/31 | 64 | 10 | 74 | 15 | 140 | 155 | ... |
| 1/ 1 | 66 | 10 | 76 | 30 | 140 | 170 | ... |
| 1/ 6 | Ether anesthesia, 60 minutes; fasting, 64 hours | | | | | | |
| 1/ 7 | 69 | 13 | 82 | 15 | 185 | 335 | ... |
| 1/ 9 | 69 | 11 | 80 | 28 | 175 | 203 | ... |
| 1/11 | 72 | 7 | 79 | 45 | 250 | 295 | ... |
| 1/13 | 65 | 11 | 76 | 30 | 200 | 230 | ... |
| 1/14 | 66 | 14 | 80 | 65 | 235 | 300 | ... |
| 1/15 | Chloroform anesthesia, 75 minutes; fasting, 51 hours | | | | | | |
| 1/16 | 78 | 15 | 93 | 85 | 63 | 148 | ... |
| 1/17 | 79 | 9 | 88 | 50 | 43 | 93 | 127 |
| 1/18 | 80 | 7 | 87 | 150 | 228 | 278 | 160 |
| 1/19 | 85 | 10 | 95 | 95 | 200 | 295 | ... |
| 1/21 | 77 | 3 | 80 | 105 | 139 | 244 | ... |
| 1/23 | 64 | 10 | 74 | 15 | 50 | 65 | ... |

TABLE 2.—*Hepatic Injury and the Elimination of Phthalein in the Urine*

| Date | Output of Phenolsulphonphthalein, per Cent | | | Output of Urine, Cc. | | | Icterus Index |
|---|---|---|---|---|---|---|---|
| | First Hour | Second Hour | Total 2 Hours | First Hour | Second Hour | Total 2 Hours | |
| | Dog 29-32; weight 18.5 Kg. | | | | | | |
| 10/17 | 72 | 3 | 75 | 90 | 200 | 290 | |
| 10/22 | 69 | 9 | 78 | 30 | 130 | 160 | |
| 10/23 | 64 | 8 | 72 | 70 | 180 | 250 | |
| 10/24 | 56 | 17 | 73 | 25 | 90 | 115 | |
| 10/25 | Chloroform anesthesia, 60 minutes; fasting, 25 hours | | | | | | |
| 10/26 | 63 | 11 | 74 | 20 | 15 | 35 | |
| 10/28 | 88 | 11 | 99 | 90 | 150 | 240 | |
| 10/29 | 78 | 19 | 97 | 130 | 100 | 230 | |
| 10/30 | 88 | 11 | 99 | 60 | 30 | 90 | |
| 10/31 | 89 | 10 | 99 | 65 | 50 | 115 | |
| 11/ 6 | 69 | 9 | 78 | 20 | 50 | 70 | |
| 11/ 8 | 70 | 10 | 80 | 60 | 135 | 185 | |
| 11/ 9 | 71 | 15 | 86 | 15 | 39 | 54 | |
| 11/11 | 75 | 10 | 85 | 29 | 91 | 120 | |
| 11/16 | 57 | 14 | 71 | ... | ... | ... | |
| | Dog 29-322; weight 17 Kg. | | | | | | |
| 7/ 2 | 67 | 10 | 77 | 50 | 100 | 150 | |
| 7/ 3 | 63 | 10 | 73 | 69 | 160 | 229 | |
| 7/12 | 69 | 9 | 78 | 148 | 270 | 418 | |
| 7/14 | 61 | 11 | 72 | 30 | 250 | 280 | 3 |
| 7/14 | Chloroform anesthesia, 75 minutes; fasting, 51 hours | | | | | | |
| 7/15 | 77 | 11 | 88 | 160 | 320 | 480 | |
| 7/16 | 72 | 19 | 91 | 105 | 290 | 395 | 20 |
| 7/17 | 78 | 11 | 89 | 140 | 140 | 280 | |
| 7/19 | 62 | 16 | 78 | 150 | 160 | 310 | 8 |
| 7/21 | 66 | 12 | 78 | 85 | 250 | 335 | 3 |
| 7/22 | 63 | 11 | 74 | 95 | 210 | 305 | |

to the liver, as indicated by the values for fibrin which were depressed, was probably not as great as in the first experiment on this dog in which the values for fibrin were very low (table 1). This statement is based on wide experience with necrosis (due to chloroform) and repair of the liver under various controlled conditions.[18]

Table 2 shows two more typical experiments with chloroform anesthesia, injury to the liver and an increased elimination of phthalein in the urine. The figures for the elimination of phthalein are higher for dog 29-32 than for dog 29-322, which would indicate a somewhat higher grade of hepatic injury, but we have no figures for the fibrin to prove it. Dog 29-32 was sick for two days during which traces of bile showed in the urine, but she recovered promptly. Dog 29-322 was not clinically ill at any time. As a general rule, younger dogs are more susceptible to chloroform poisoning than older animals, and

TABLE 3.—*Mild Hepatic Injury and the Elimination of Phthalein in the Urine of Dog 29-227; Weight, 16 Kg.*

| Date | Output of Phenolsulphonphthalein, per Cent | | | Output of Urine, Cc. | | | Fibrin, Mg. per 100 Cc. |
|---|---|---|---|---|---|---|---|
| | First Hour | Second Hour | Total 2 Hours | First Hour | Second Hour | Total 2 Hours | |
| 1/11 | 60 | 9 | 69 | 55 | 210 | 265 | 298 |
| 1/14 | 64 | 8 | 72 | 95 | 278 | 373 | 294 |
| 1/16 | 55 | 9 | 64 | 20 | 160 | 180 | ... |
| 1/17 | 63 | 10 | 73 | 78 | 235 | 313 | ... |
| 1/17 | Chloroform anesthesia, 75 minutes; fasting, 51 hours | | | | | | |
| 1/18 | 69 | 10 | 79 | 90 | 208 | 298 | 346 |
| 1/19 | 80 | 9 | 89 | 120 | 190 | 310 | ... |
| 1/21 | 78 | 10 | 88 | 50 | 195 | 245 | ... |
| 1/23 | 65 | 6 | 71 | 3 | 58 | 61 | ... |
| 1/28 | 55 | 16 | 71 | 60 | 309 | 369 | ... |
| 2/ 7 | 66 | 13 | 79 | 58 | 258 | 316 | ... |
| 2/ 9 | 67 | 10 | 77 | 60 | 220 | 280 | ... |

a longer period of fasting usually renders a dog more susceptible, but there are individual differences which at present we cannot explain. The icterus index in the second experiment (table 2) showed a rise that is invariably present in cases of hepatic necrosis of moderate or slight grade. In this dog the elevated elimination of phthalein lasted only three days.

Table 3 shows a mild case of hepatic injury due to chloroform, as indicated by the rise in the figures for fibrin. This dog (29-227) took the chloroform anesthesia poorly and was given less chloroform than usual, which may explain the slight hepatic injury associated with seventy-five minutes' anesthesia. We have repeatedly observed that slight hepatic necrosis, like necrosis of tissue elsewhere (sterile abscess), will cause a rise in the blood fibrin, whereas moderate or severe hepatic

18. Davis, N. C.: Liver Regeneration Following Chloroform Injury as Influenced by Various Diets, Arch. Int. Med. **23**:711 (June) 1919.

necrosis caused by chloroform will cause a moderate or notable decrease in blood fibrin, due in part to hepatic dysfunction and insufficiency. The rise in the elimination of phthalein was only moderate and definitely less than the figures recorded in tables 1 and 2. None of these dogs showed an albuminuria before or after the chloroform anesthesia.

In this group of experiments urea clearance tests were performed, but owing to inexperience with the methods, we have not included them in this report. In general, however, our results suggested an increased clearance after the administration of chloroform. As a rule, the blood urea showed a drop. As far as we know, there is no report in the literature on the variations from normal of the urea clearance test in cases of hepatic damage with normal kidneys. We hope to give this subject further study.

In order to bring additional evidence that the liver in dogs is impaired in its ability to excrete phthalein after chloroform anesthesia, a different type of experiment was performed.

The normal level of the output of phthalein was determined. The dog was then starved and given chloroform in the usual manner. The excretion of phthalein in the urine was determined twelve and thirty-six hours after the administration of chloroform, and was found to be increased during the two hour period from the normal of from 70 to 75 per cent to 88 per cent, as in similar experiments already tabulated. Forty-eight hours following the chloroform anesthesia, the dog was given a general ether anesthesia, a cannula was inserted into the common duct, and the bile and urine were collected over a two hour period following the injection of 60 mg. of phthalein. The flow of bile was greatly decreased, only 2 cc. being collected, and no trace of phthalein could be demonstrated in it. The kidneys excreted 40 cc. of urine, which contained 25 per cent of the dye. The dog was killed under ether anesthesia. At autopsy, the liver showed typical marked central necrosis, but the other organs were normal. An alcoholic extract of macerated liver gave no trace of the phthalein, whereas an extract of the kidneys contained large quantities of it. In similar experiments, only without a preceding chloroform anesthesia, dogs under ether anesthesia showed a flow of bile containing from 9 to 10 per cent of the phenolsulphonphthalein originally injected.

Phosphorus poisoning causes a characteristic hepatic injury, but the experiments are difficult to control with the accuracy possible in experiments on chloroform poisoning. The usual difficulties were encountered in this type of experiment, and we record no experiment in detail as the change in the elimination of phthalein was much less marked. In several dogs with moderate phosphorus poisoning, the elimination of phthalein rose somewhat above control levels, but not to the same extent noted in hepatic injury due to chloroform.

*The Elimination of Phthalein in the Bile of Normal Dogs Under Ether Anesthesia.*—Obviously dogs under ether anesthesia are not strictly normal, nor are dogs with biliary fistulas of many weeks' dura-

tion, yet from experiments on both types evidence as to how much phenolsulphonphthalein is eliminated by the liver may be gained. The following two experiments give evidence that the normal dog under ether anesthesia will eliminate 10 per cent or more of the injected phthalein through the bile during a period of two hours.

EXPERIMENT A (dog 29-4).—At 10:25 a. m., 150 cc. of bile was given by stomach tube to increase the flow of bile. At 11:25 a. m., the administration of ether was begun. A cannula was inserted in the common bile duct and in the urinary bladder. At 12:38 p. m., 60 mg. of phenolsulphonphthalein was injected into the jugular vein, followed by 300 cc. of physiologic solution of sodium chloride injected slowly. At 12:45 p. m. the phthalein made its first appearance in the bile, and at 12:48 p. m., its first appearance in the urine. At 2:38 p. m., the dog was killed under ether anesthesia.

Examination of 30 cc. of urine two hours after the injection of phenolsulphonphthalein showed 74 per cent of the dye. Five cubic centimeters of bile from the cannula returned 4 per cent of phenolsulphonphthalein, while 15 cc. of bile from

TABLE 4.—*Biliary Fistula and the Elimination of Phthalein*

| | | Phenolsulphonphthalein | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Output, per Cent | | | Flow of Urine, Cc. | | Biliary Flow, Cc. in 6 Hours |
| Dog * | Date | Injected Intravenously, Mg. | Urine 2 Hours | Urine 6 Hours | Bile 6 Hours | 2 Hours | 6 Hours | |
| 29-8 | 6/12 | 60 | 95 | 99 | Trace | 245 | 645 | 18 |
| | 6/13 | 60 | 88 | 93 | Trace | 550 | 970 | 11 |
| | 6/14 | 60 | 83 | 89 | Trace | 140 | 235 | 27 |
| 29-169 | 6/12 | 60 | 80 | 84 | 7 | 285 | 435 | 14 |
| | 6/13 | 60 | 82 | 85 | 9 | 302 | 418 | 15 |
| | 6/14 | 60 | 83 | 86 | 7 | 250 | 415 | 33 |

* An operation for biliary fistula was performed on dog 29-8 on February 20 and on dog 29-169 on February 25.

the gallbladder returned 6 per cent. The total recovery of phenolsulphonphthalein was 84 per cent of the amount originally injected into the dog.

EXPERIMENT B (dog 29-244).—At 1:30 p. m., 150 cc. of bile was given by stomach tube to dog 29-244, which weighed 5 Kg. At 2 p. m., anesthesia was begun by the injection of iso-amyl-ethyl barbituric acid, intraperitoneally, supplemented with ether. Cannulas were inserted into the common duct and the urinary bladder, and the cystic duct was ligated. At 2:50 p. m., 60 mg. of phenolsulphonphthalein was injected intravenously. At 2:58 p. m., it made its first appearance in the bile, and at 3 p. m., its first appearance in the urine; there was, however, a lack of diuresis. At 4:50 p. m., the dog was killed under ether anesthesia.

Two hours after the injection of phenolsulphonphthalein had been made in the total collection of 50 cc. of urine there was 67 per cent of phthalein. In the total collection of 8 cc. of bile there was 9 per cent of the dye. The bile of the gallbladder did not show phthalein. There was, therefore, a total recovery of 76 per cent of the phenolsulphonphthalein injected.

At autopsy, the tissue of the liver and the kidney of both dogs was found to be normal in gross and in histologic sections.

To supplement the short experiments on the elimination of phenolsulphonphthalein in the bile during ether anesthesia, we utilized dogs

with closed sterile biliary fistulas. These dogs were operated on by Dr. H. P. Smith according to a technic described elsewhere.[19] Table 4 shows that biliary fistulas may vary widely in their capacity to eliminate phenolsulphonphthalein in the bile. It is known that these fistulas may lose their capacity to eliminate dyes. Both these dogs had been under observation with a daily collection of bile for about four months. In some instances the presence of infection in the biliary passages may be partly responsible for the difference. Whatever the cause, from the biliary fistula of one dog there was but a trace of phthalein in the bile and a distinctly high output in the urine. In the biliary fistula of

TABLE 5.—*Obstruction of the Bile Duct and the Elimination of Phthalein in the Urine*

| Date | Output of Phenolsulphonphthalein, per Cent | | | Output of Urine, Cc. | | | Icterus Index |
|---|---|---|---|---|---|---|---|
| | First Hour | Second Hour | Total 2 Hours | First Hour | Second Hour | Total 2 Hours | |
| | Dog 29-227: weight 16 Kg. | | | | | | |
| 5/19 | 66 | 8 | 74 | 60 | 250 | 316 | .. |
| 5/21 | 61 | 11 | 72 | 60 | 285 | 340 | .. |
| 5/23 | 62 | 9 | 71 | 105 | 205 | 310 | 4 |
| 5/24 | Common duct ligated | | | | | | |
| 5/26 | 80 | 5 | 85 | 18 | 165 | 183 | 24 |
| 5/28 | 74 | 12 | 86 | 38 | 360 | 434 | 70 |
| 5/30 | 78 | 10 | 88 | 87 | 420 | 507 | 70 |
| 6/ 2 | 71 | 13 | 84 | 93 | 214 | 307 | 70 |
| 6/ 4 | 74 | 10 | 84 | 57 | 170 | 227 | .. |
| 6/ 9 | 81 | 12 | 93 | 33 | 124 | 157 | .. |
| 6/10 | 67 | 17 | 84 | 65 | 198 | 263 | .. |
| 6/16 | .. | .. | 91 | ... | ... | 250 | .. |
| | Dog 29-307: weight 13 Kg. | | | | | | |
| 7/15 | 66 | 7 | 73 | 190 | 70 | 260 | .. |
| 7/17 | 67 | 9 | 76 | 130 | 255 | 385 | .. |
| 7/18 | 66 | 10 | 76 | 90 | 225 | 315 | 4 |
| 7/19 | Common duct ligated | | | | | | |
| 7/21 | 67 | 11 | 78 | 109 | 46 | 155 | 8 |
| 7/22 | 76 | 11 | 87 | 133 | 52 | 185 | 20 |
| 7/24 | 57 | 33 | 90 | 70 | 79 | 149 | 40 |
| 7/26 | 72 | 13 | 85 | 132 | 130 | 262 | 40 |
| 7/29 | 81 | 12 | 93 | 190 | 85 | 275 | 45 |
| 8/ 1 | 74 | 9 | 83 | 200 | 70 | 270 | 70 |
| 8/ 5 | 71 | 12 | 83 | 85 | 140 | 225 | 70 |

dog 29-169 (table 4), the output of phthalein was between 7 and 9 per cent in the bile and between 80 and 83 per cent in the urine. On June 14, both dogs were given bile by mouth, with a moderate cholagogue effect which did not modify the elimination of phthalein in the biliary fistula.

*Obstruction of the Bile Duct.*—Dogs with obstructed common ducts show a definite rise in the elimination of phthalein by way of the kidneys (table 5). These figures are not quite as high as they are in dogs with marked hepatic injury due to chloroform, and to explain

19. Smith, H. P.; Groth, A. H., and Whipple, G. H.: J. Biol. Chem. **80**:659, 1928.

the difference two factors are suggested: 1. In heavily pigmented urine, the phthalein is more difficult to read, and the method of separation of the bile pigments carries down a little phthalein. 2. Even in an obstructed common duct some phthalein is taken into the epithelium of the liver and the bile canaliculi.

We noted the expected rise in the icterus index. After completion of these observations the dogs were killed with ether. Autopsy showed the usual picture associated with continued biliary obstruction. The common bile ducts were completely occluded by the ligatures. Except for bile stains, the kidneys and viscera were normal.

Of similar nature is an experiment on a dog with an Eck fistula in which a closed sterile biliary fistula had been produced by Dr. H. P. Smith in connection with other experimental work. After a time, biliary obstruction developed in this dog (table 6), due to blocking of

TABLE 6.—*Eck Fistula with Partial Obstruction of the Bile Duct and the Elimination of Phthalein in Dog 29-14; Weight, 13 ± Kg.*

| Date | Output of Phenolsulphonphthalein, per Cent | | | Output of Urine, Cc. | | |
|---|---|---|---|---|---|---|
| | First Hour | Second Hour | Total 2 Hours | First Hour | Second Hour | Total 2 Hours |
| 2/11 | 91 | 5 | 96 | 70 | 86 | 156 |
| 3/ 3 | 87 | 4 | 91 | 80 | 75 | 155 |
| 3/ 4 | 67 | 15 | 82 | 90 | 240 | 330 |
| 3/ 5 | 77 | 6 | 83 | 85 | 100 | 185 |
| 3/ 6 | Ether anesthesia, 120 minutes | | | | | |
| 3/24 | 90 | 7 | 97 | 55 | 215 | 270 |
| 4/ 4 | 80 | 5 | 85 | 165 | 240 | 405 |
| 4/ 8 | 84 | 3 | 87 | 160 | 115 | 275 |
| 4/29 | 78 | 6 | 84 | 100 | 131 | 281 |

the flow of bile in the tube of the fistula. The dog remained in good health and eventually a partial drainage of bile was established into the duodenum. Preoperative, control tests made with phthalein were not available.

In this dog the elimination of phthalein by the way of the kidney was high (table 6), and held about the same level as that noted in the dogs with obstructed common bile ducts. This was to be expected in spite of a slight drainage of bile during the last part of the experiment. A liver with an Eck fistula is known to be subnormal functionally, and there is less elimination through the liver on this account. On March 6, during the period of ether anesthesia (table 6), the bile ducts were explored. The dog died on March 30. Autopsy showed the atrophied liver usually seen in the case of an Eck fistula, with a little fatty change. The kidneys were normal.

*The Effect of Cholagogue and the Oral Administration of Phenolsulphonphthalein.*—We suspected that an active cholagogue effect

might sweep more phenolsulphonphthalein into the bile than was usual and therefore decrease the urinary output. We have already noted (table 4) that in dogs with biliary fistulas, whether a cholagogue is used or not, there is no difference in the elimination of phthalein in the bile. In normal dogs carefully standardized for the elimination of phthalein by way of the kidney, we have repeatedly tested the influence of large doses of bile given by mouth. Whether or not there may be a slight increase in the output of phthalein in the bile under these conditions, there is a uniformly normal urinary output of phthalein. These dogs were given 150 cc. of bile by stomach tube one hour before the phthalein was given intravenously. The phthalein eliminated in the urine was always within control limits.

The gastro-intestinal tract absorbs a limited amount of phenolsulphonphthalein given by mouth. In a series of dogs in which 30 mg. of phenolsulphonphthalein was given by stomach tube, only from 3 to 5 per cent appeared in the urine and only traces in the feces. Obviously, intestinal absorption plays no rôle in any of the reactions that we have studied. In a normal dog, granting 20 per cent elimination of phthalein by way of the bile, we could expect only 5 per cent of this amount to be absorbed. This amount of phenolsulphonphthalein is within the limits of error of any method of analysis.

## COMMENT

It is obvious that the liver of the normal dog excretes from about 10 to 15 per cent of the usual dose of phenolsulphonphthalein, and when this route of escape is blocked, the surplus appears in the urine, giving figures proportionately greater, as recorded in the various tables cited. Phthalein which escapes into the gastro-intestinal tract is absorbed only to a limited degree—not in excess of 5 per cent of the amount secreted into the duodenum, so that reabsorption from the bile can be dismissed as a factor of no importance.

Clinically, this reaction may have some significance, as an unusually high elimination of phthalein in the urine would suggest an abnormality in the liver. When abnormalities are present in both the liver and the kidney of a patient, careful study might solve the puzzle, but judgment would indeed be difficult. However, if the clinician understood these possibilities, he would not be led astray by an unusual elimination of phthalein in the urine.

## SUMMARY

From our experiments it is clear that in dogs with necrosis of the liver due to chloroform poisoning there is a distinct rise in the elimination of phenolsulphonphthalein by the normal kidney. A rise

in the elimination of phthalein from a control level of from 75 to 78 per cent, to from 90 to 97 per cent may be noted. With repair of the hepatic injury, the elimination of phthalein returns to normal. Phosphorus poisoning gives a similar but less striking reaction.

With experimental biliary obstruction in the dog, the same general reaction is noted, with a definite increase in the elimination of phenolsulphonphthalein by the normal kidney.

After hepatic injury due to chloroform, the dog's liver does not remove phenolsulphonphthalein from the blood stream and does not excrete it in the bile, whereas in a normal dog, the liver removes much phthalein from the blood, and about 10 per cent of the injected phthalein may be recovered from the bile within two hours.

A chronic biliary fistula and an Eck fistula may permit a smaller excretion of phenolsulphonphthalein in the bile and a corresponding rise in the elimination of phthalein in the urine.

There is no evidence that cholagogue, whether in the normal dog or in one with a biliary fistula, increases the elimination of phthalein by way of the bile, and consequently the urinary excretion of phthalein is unchanged.

Phenolsulphonphthalein given by mouth is absorbed and reappears in the urine only in quantities equal to from 3 to 5 per cent of the phthalein administered. Reabsorption, therefore, is a negligible factor when applied to the phenolsulphonphthalein eliminated through the bile into the duodenum.

From these experiments and the observations of other workers, it may be concluded that the elimination of phthalein by the liver and kidney under these conditions is identical in the dog and man.

Clinically, an unusually high renal elimination of phenolsulphonphthalein should suggest pathologic changes in the liver. Combined renal and hepatic disease calls for cautious analysis of the renal elimination of phenolsulphonphthalein.

# TUMORS OF THE SUPRARENAL GLAND WITH SPECIAL REFERENCE TO CARCINOMA OF THE CORTEX

## REPORT OF A CASE *

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AND
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CHICAGO

Four syndromes are recognized as associated with changes in the suprarenal gland. The first, Addison's disease, is due to hypofunction of the suprarenal cortex as a result of disease, usually tuberculosis. This condition is a well recognized entity and need not be discussed here. The second picture is that seen as a result of tumor of the suprarenal medulla; its characteristic features result from metastatic phenomena, as described by Hutchison and Pepper. These will be discussed more fully in the section of this paper on pathology. The third is the recently described picture of cytotoxic degeneration of the suprarenal cortex, and may be found described in recent periodicals. The fourth syndrome is that described by Gallais [1] as "le syndrome génito-surrénal," and is seen in tumors of the suprarenal cortex with neoplastic tendencies.

To acquaint the physician better with this syndrome we shall report a case and emphasize the characteristic symptoms and signs of the picture. The desirability of early recognition of the tumor is obvious, especially in the light of recent reports on the surgical removal of tumors of the suprarenal capsule, with complete recovery.

### REPORT OF A CASE

*History.*—M. R., a white girl, aged 13, entered the service of Dr. A. Strauss complaining of pain in the chest and the abdomen, dermatitis, indigestion and epileptiform attacks.

She had felt well until eight weeks before, when she was seized with a severely sharp pain in the lower right side of the chest. A few minutes later she complained of pain in the abdomen, which was not a radiation from the pain in the chest. No nausea or vomiting occurred. Constipation had continued to the time of admission. The abdominal pain had recurred two or three times daily after the ingestion of any food.

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* From the Medical Service and Stomach Study Group, Michael Reese Hospital.

1. Gallais, Alfred: Le syndrome génito-surrénal; étude anatomo-clinique, Thèse, Paris, 1912, no. 225.

The dermatitis was of about five months' duration. It was an acneform rash, covering the face and trunk and not affecting the extremities.

Menstruation, which had started when the patient was 12½ years of age, was of the regular twenty-eight day type, each period lasting between three and four days. The menses had ceased three months before admission. Other facts in the history were irrelevant.

*Physical Examination.*—The patient was extremely well developed and well nourished and did not seem to be acutely ill. Although only 13 years of age, she had the appearance of a person of 19 or 20.

A papular and pustular lesion was present on the face, the neck and the anterior portion of the chest and extended over the entire back to the buttocks. There were many comedones on the face, and moderate dermatographia. The facies was negroid, which was accentuated by hirsuties.

The breasts were slightly developed. The genitalia showed an abnormal growth of pubic hair, with a distinct tendency to masculine distribution.

The left border of the heart was 11 cm. to the left of the midsternal line in the fourth interspace, and 3 cm. to the right. The heart was probably displaced upward by a combination of enlarged liver and distended abdomen, rather than being itself enlarged. The tones were regular and of good intensity. There was a soft systolic blowing murmur at the base of the left lung. The blood pressure was 158 systolic and 85 diastolic.

The abdomen was full and somewhat distended. There was no fluid or rigidity.

The upper border of the liver reached the fourth rib, while the lower border was at the level of the umbilicus; the edge was felt to the left as far as the left nipple line. The edge and surface were irregular, there were several palpable nodules, and the consistency was increased.

The spleen was not palpable, and the kidneys were not felt.

The Wassermann and Kahn reactions were negative; the blood count showed leukocytosis, with an increase in polymorphonuclears. Chemical examination of the blood showed that it was normal, and the icteric index and van den Bergh reactions were negative. On two occasions the urine showed albumin and a few pus cells. A complete series of roentgenograms of the gastro-intestinal tract failed to disclose a pathologic process. A roentgenogram showed the right kidney to be somewhat enlarged, but with a smooth outline.

*Course.*—During the patient's stay in the hospital, the liver seemed to be enlarging downward, particularly to the left. It was questionable whether or not the spleen was palpable. The right lobe of the liver seemed to be irregular, and had a stratified, steplike anterior surface.

A blood smear disclosed about 5 per cent immature leukocytes, most of them myelocytes.

Epigastric fulness and pain seemed to become more severe from day to day, but there was no qualitative distress from food. The patient was given hourly feedings of milk and cream, with additional small feedings of a soft diet, three times a day. She refused food so persistently that a duodenal tube was introduced for feeding.

About the eighth day after admission, the patient began to look more acutely ill. At 4 p. m. her temperature rose above normal for the first time, reaching 100 F., and her pulse rate was 116.

Little progress was made in the formation of a diagnosis. The icteric index and van den Bergh reaction practically ruled out hypertrophic biliary cirrhosis. The negative Wassermann reaction spoke against syphilitic cirrhosis or hepatitis.

The possibility of a myelogenous leukemia was considered in view of the finding of immature leukocytes; however, either a derangement in the physiology of the liver or leukocytosis might explain the presence of an occasional myelocyte. A vascular accident in a congenitally malformed liver might constitute the underlying pathology of the case. Cystic adenoma of the liver was also considered as a possibility. A possible endocrine disturbance was considered to explain the patient's overgrowth and the masculine distribution of hair.

One week after admission, signs and symptoms of intra-abdominal hemorrhage developed, and death occurred seven hours later.

*Postmortem Examination.*—Autopsy was performed by Dr. Otto Saphir. The head was covered with a good growth of coarse, kinky, black hair. There was a marked growth of pubic hair. The skin was sallow. There were many discrete

Fig. 1.—Tumor of the suprarenal gland.

small pustules on the forehead, chin and chest. The breasts were small, but the nipples and areolae were well developed. The abdomen was somewhat distended. The body from the pelvis down had the development of a 20 year old woman. The vulva was edematous and there was a slight degree of edema of the lower extremities.

The pleural and pericardial cavities did not contain excessive amounts of fluid or adhesions. The peritoneal cavity was filled with about 1,500 cc. of bloody fluid. The liver extended to the level of the umbilicus. A large, spherical mass having a diameter of about 17 cm. was palpable in the region of the left kidney.

The heart was about normal in size. There were slight hypertrophy and dilatation of the left ventricle. The auricles, the right ventricle and the valvular apparatus appeared normal. Changes were not noted in the aorta.

The lungs were nearly normal in size, soft and air containing. On the visceral pleurae a few firm, raised, grayish nodules, having an average diameter of 2 mm., were found, which, on section, presented gray, granular surfaces.

Sections of the lungs were deep pink. There were a few areas that were slightly raised and that presented a grayish granular appearance. The larynx and trachea were normal.

The liver was markedly enlarged and weighed about 3 Kg. There was a tear at the inferior border of the left lobe, about 3 cm. in length. Many irregularly circular, firm, raised, pinkish-gray areas were seen beneath the capsule on all the surfaces of the liver. The tissue between these nodules was bluish red in areas and yellowish brown in other portions. On section, numerous raised, firm, yellowish-gray, granular masses were seen throughout. They varied in size from 1 to about 3 cm. The intervening tissue was yellowish brown. In some areas the central zones appeared as grayish-red dots, many of which were fused by confluence to form a prominent bluish-red network.

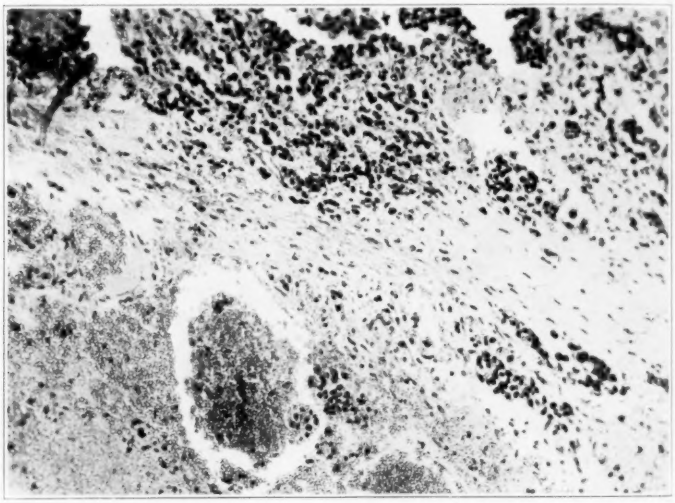

Fig. 2.—Histologic section of the tumor showing cells and areas of necrosis and degeneration.

The spleen was normal in size. The capsule was smooth and bluish gray, and on section the cut surface was dark red, and numerous malpighian corpuscles could be seen.

The site of the left kidney was completely replaced by a tumor mass measuring 17 by 13 by 7 cm. This mass was covered by a thin fibrous capsule, which when separated disclosed the left kidney lying in a medial and posterior position. The left kidney was somewhat smaller than normal and was apparently compressed lateromedially. The capsule of the kidney was not involved by the tumor. It stripped with ease, revealing the surfaces of the kidney to be smooth and pale brown. The stellate veins were hyperemic. On section, the architecture of the cortex and the medulla was distinct. The pyramids were somewhat hyperemic. The right kidney appeared normal. The renal pelves, ureters and urinary bladder did not show gross changes.

The tumor was fairly soft and had a lobulated appearance. On section, broad bands of connective tissue were seen which divided the tumor into several large lobes. In areas this connective tissue appeared to be hyalinized, and in other portions, hemorrhagically discolored. The tumor tissue was yellowish gray, soft and very friable. It had a granular architecture. In portions the tumor tissue was compact and firm, while in other portions it was mushy.

The right suprarenal gland appeared normal.

The lymph nodes throughout the peritoneal cavity and those attached to the pericardial sac showed marked enlargement. About the hilus of the liver and attached to the serosa of the neck of the gallbladder were several lymph nodes. The nodes had an average diameter of about 1 cm. Most of them were soft and, on section, presented yellowish-gray, granular, cut surfaces.

The thyroid gland did not show gross pathologic changes.

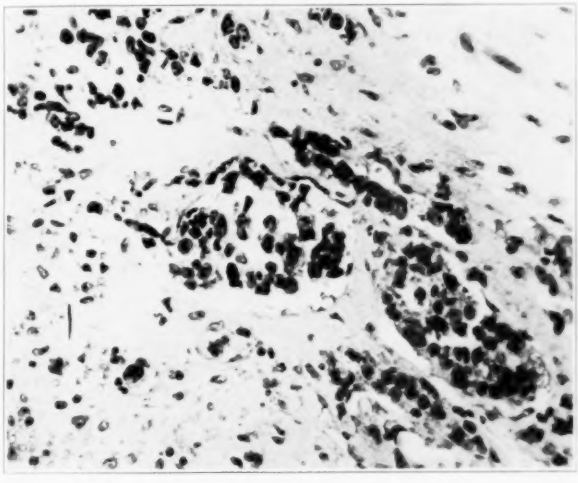

Fig. 3.—Microscopic section of the tumor showing carcinoma cells and areas of necrosis and degeneration.

The uterus appeared to be maturely developed and nulliparous. The tubes and ovaries were normal.

The anatomic diagnosis was: primary carcinoma of the left suprarenal gland with metastases to the pleurae, the liver and the peritoneal and mediastinal nodes; hemoperitoneum; slight hypertrophy and dilatation of the left ventricle; chronic passive hyperemia of the liver, lungs, kidneys and intestines; fat infiltration of the liver; precocious development; early bronchopneumonia, and virilism.

Microscopic examination was made by Dr. Otto Saphir. Sections of the left suprarenal gland showed a marked new formation of cells in some of the fields. Most of these were apparently epithelial. They were very large and showed granular cytoplasm. Many cells were hexagonal, while others appeared more square. Some of the cells resembled those of the zona fasciculata. In general, the cells varied in size, form and staining quality. The nuclei stained a deep blue, and

most of them were vesicular and eccentrically situated. Many mitotic figures were found invading the tissue. Other areas showed an abundant amount of necrosis and hemorrhage, with only remnants of cells. Other fields showed cells invading the walls of veins, while in others the veins were filled with tumor cells. The sections showed little stroma between the tumor cells.

Microscopic examination of the lungs showed a few more or less circumscribed areas with an invasion of tumor cells similar to those in the left suprarenal gland. Some of these vessels in the section were filled with tumor cells.

Sections of the heart showed the muscle fibers to be somewhat larger than normal. A few fields showed an extension of the epicardial fat tissue into the myocardium.

Sections of the liver showed large nodules that were made up entirely of tumor cells. The necrosis here was slight, and therefore the shape of the tumor cells could be studied to great advantage. The surrounding liver tissue was markedly compressed.

Sections of the right suprarenal gland showed a large cortical adenoma. Pathologic changes were not noticeable. A section of the hypophysis did not show histologic changes.

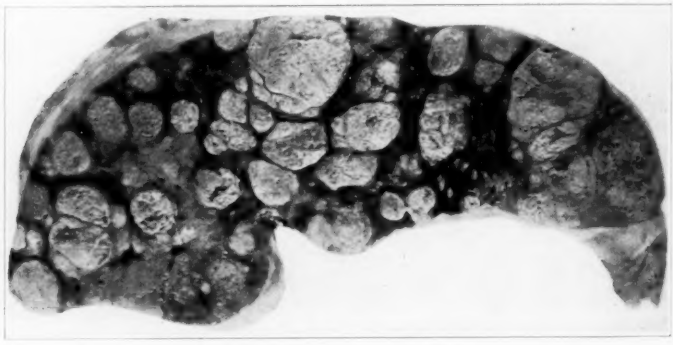

Fig. 4.—Metastasis to the liver.

## SYMPTOMS

Though individual cases present marked variability in the character and intensity of the symptoms which they present, the picture of suprarenal cortical tumor is always so characteristic that the only excuse for failure to make an early diagnosis is lack of familiarity with the syndrome which Gallais has appropriately named "le syndrome génito-surrénal."

The symptoms vary, first, depending on the age at which the tumor develops. Gallais, for instance, described four forms: (1) congenital, (2) early acquired, (3) menstrual and (4) obstetric. Apert [2] described

2. Apert, E.: Dystrophies en relation avec des lésions de capsules surrénales, hirsutisme et progenia, Bull. Soc. de pediat. de Paris **12**:501, 1901; Sur l'hirsutisme, Bull. et mém. Soc. méd. d. hôp. de Paris **49**:131, 1925.

five forms. Hoskins[3] simplified the classification somewhat, and described three forms: (1) hypertrophy of the suprarenal cortex during fetal life, producing pseudohermaphroditism (illustrative of this form is a case reported by Quinby,[4] in which he described a girl who was raised as a boy because of the masculine status and genitalia); (2) hypertrophy during early postnatal life, resulting in the production of pubertas praecox, and (3) hypertrophy after puberty, producing virilism or hirsutism.

Whereas other glandular dysfunctions, particularly those resulting from tumor of the pineal gland and alterations of the sexual glands, may result in the abnormal growth of hair, marked physical development and the premature development of secondary sexual characteristics, other symptoms produced by hypertrophy of the suprarenal cortex

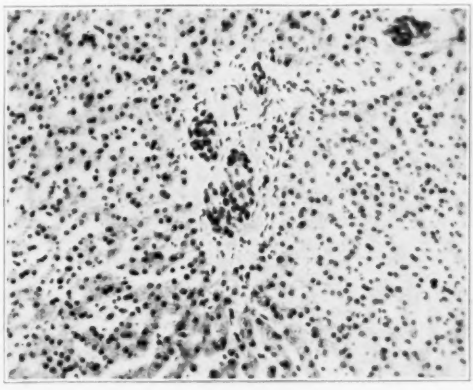

Fig. 5.—Microscopic section showing metastasis to the liver and periportal spaces.

serve to differentiate the "syndrome génito-surrénal" from other causes of hypertrichosis and virilism.

The sexual alterations produced by hypertrophy of the suprarenal cortex are always in the direction of masculinization—toward the adult male type. Thus, the young female becomes pseudohermaphroditic, with an enlargement of the clitoris, an early growth of pubic hair and a tendency for its distribution to assume the masculine type. The young male exhibits precocious puberty, with sexual precocity. No evidence

3. Hoskins, R. G.: Hypergenitalism and Hypogenitalism, in Abt, I. A.: Pediatrics, Philadelphia, W. B. Saunders Company, 1924, p. 745.

4. Quinby, W. C.: A Case of Pseudo-Hermaphroditism, with Remarks on Abnormal Function of the Endocrine Glands, Bull. Johns Hopkins Hosp. **27**:50, 1916.

has been found, however, to indicate an increase in spermatogenesis; rather, the reverse seems to be true. The type of sexual alteration produced by hypertrophy in early adult life is well illustrated by our case and by that described by Gordon Holmes.[5] His case was that of a large, slowly growing tumor of the right suprarenal cortex in a young woman. The tendencies toward the loss of feminine sexual characteristics with a change toward masculinization were exhibited as follows: (1) alterations in the sexual organs, with atrophy of the uterus and overgrowth of the clitoris; (2) disturbance of the sexual functions, especially amenorrhea; (3) changes in the secondary sexual characteristics, with an abnormal growth of hair, atrophy of the breasts, alterations

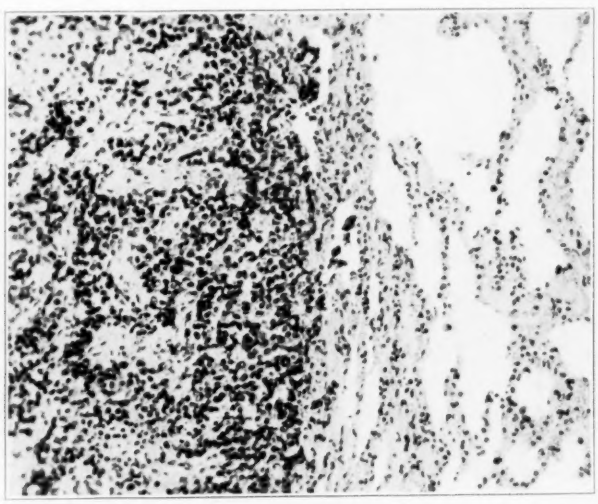

Fig. 6.—Microscopic section showing metastasis to the lung.

in the distribution of fat and the development of masculine limbs, and (4) psychic changes, with loss of erotic feelings and lack of modesty.

An important observation in the genito-suprarenal syndrome is the presence of hypertension. Oppenheimer and Fishberg [6] called particular attention to this symptom in association with suprarenal tumors. It will be noted that on admission to the hospital our patient, a girl of 13, had a blood pressure of 158 systolic and 85 diastolic, with no evidence

5. Holmes, Gordon: A Case of Virilism Associated with a Suprarenal Tumor: Recovery After Its Removal, Quart. J. Med. **18**:143, 1924-1925.

6. Oppenheimer, B. S., and Fishberg, A. M.: The Association of Hypertension with Suprarenal Tumors, Arch. Int. Med. **34**:631 (Nov.) 1924.

of nephritis. The reason for the production of hypertension is obscure, for Tokumitsu [7] has shown that the injection of suprarenal cortex into animals, unlike the effect of medullary extract, causes a drop in the blood pressure.

Pigmentation is frequently found associated with tumors of the suprarenal cortex. It differs in distribution from that found in Addison's disease, and is not a constant observation. Rough skin and an acneform eruption, especially over the trunk and face, are also fairly frequent symptoms. Attention was called to this condition by Jump, Beates and Babcock,[8] who analyzed 18 cases of tumor of the suprarenal cortex in

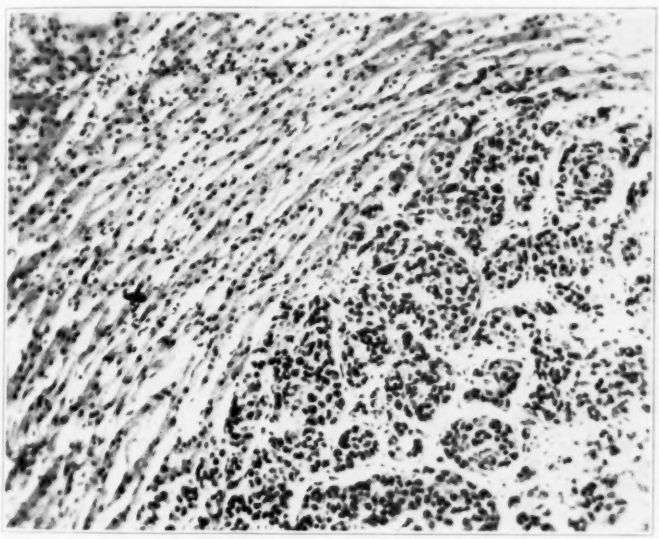

Fig. 7.—Microscopic section showing metastasis to the liver.

1914. It was present in our case. Some patients display mental precocity. The majority are, however, mentally dull, with a diminution, particularly in females, in what would appear to be an instinctive sense of modesty. Riesman [9] called attention to the occasional occurrence of gastric dis-

7. Tokumitsu, Y.: On the Function of the Suprarenal Cortex and Its Relation with Other Endocrine Glands, Japan M. World **3**:212, 1923.

8. Jump, H. D.; Beates, N., and Babcock, W. W.: Precocious Development of the External Genitals Due to Hypernephroma of the Adrenal Cortex, Am. J. M. Sc. **147**:568, 1914.

9. Riesman, D.: Diseases of the Adrenal Glands, in Christian, H. A., and Mackenzie, J.: The Oxford Medicine, New York, Oxford University Press, 1920, vol. 3, p. 791.

orders and vomiting, even in the absence of metastatic causes for such complaints. Finally, there is a variety of symptoms which may result from metastatic growths in the kidneys, liver, brain, lungs, etc., and which obviously vary greatly in individual patients.

Experimentation on animals has resulted in the accumulation of a few facts concerning hyperfunction of the suprarenal cortex. Thus, Stilling [10] has shown that the adrenals are enlarged in male rabbits during breeding. Guieysse [11] found enlargement of the adrenal glands in pregnant guinea-pigs. Schenk [12] and Cecca [13] found an increased amount of cortex in castrated rabbits—a condition that they took to be compensatory. In studying the cause of retarded sexual development in certain persons, Karakascheff [14] constantly found an atrophy of the suprarenal glands. Berner [15] described a hen which had spurs and a comb, never laid eggs and had the strutting gait of a cock, but which never crowed. It was found to have a tumor of the right adrenal cortex with metastases to the peritoneum, lungs and ovary. Fordyce and Evans [16] stated that sexual changes of two types occur, depending on whether the tumor is in a male or a female. If in the latter, all changes in the secondary sexual characteristics tend toward masculinization; whereas in the former, an intensification of male characteristics occurs, but with no increase of potency. Lack of spermatogenesis in such cases has been noted by Fordyce and Evans, Adams,[17] Guthrie and Emery [18] and Tschernobrow.[19]

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10. Stilling, H.: Zur Anatomie der Nebennieren, Arch. f. mikr. Anat. **52**: 176, 1898.

11. Guieysse, A.: La capsule surrénale du cobaye, J. de l'anat. et de la physiol. **37**:312, 1901.

12. Schenk, F.: Ueber die Veränderungen der Nebennieren nach Kastration, Beitr. z. klin. Chir. **67**:316, 1910.

13. Cecca, M.: Glandes à secretion interne étudiées au point de vue chirurgical, Presse méd. **12**:301, 1904.

14. Karakascheff, K. I.: Beiträge zur pathologischen Anatomie der Nebennieren: Atrophie, vikarierende hypertrophie Tuberkulose, Beitr. z. path. Anat. u. z. allg. Path. **36**:401, 1904.

15. Berner, O.: Suprarenal Virilism, Norsk mag. f. lægevidensk. **84**:849 (Oct.) 1923.

16. Fordyce, A. D., and Evans, W. H.: Suprarenal Virilism, Quart. J. Med. **22**:557 (July) 1929.

17. Adams, Charles: A Case of Precocious Development Associated with a Tumor of the Left Adrenal Body, Tr. Path. Soc. London **56**:208, 1905.

18. Guthrie, L., and Emery, W. D'Este: Precocious Obesity, Premature Sexual and Physical Development and Hirsuties in Relation to Hypernephroma and Other Morbid Conditions, Tr. Clin. Soc. London **40**:175, 1907.

19. Tschernobrow, E.: Ueber eine Geschwulst der Nebennieren bei einem 11 jährigen Knaben mit früh-zeitigen Geschlechtsentwicklung, Thesis, Zurich, 1919.

Various theories have been proposed to account for the secondary sexual manifestations accompanying suprarenal tumor. 1. Bulloch and Sequeira,[20] Glynn [21] and others expressed the opinion that tumor of the cortex results in accentuation of the normal physiologic function of that portion of the organ. 2. Gallais [1] expressed the belief that the sexual changes result from a pluriglandular disturbance, with hyperfunction of the cortex affecting the ovary in the female. 3. Blanchard [22] believed the cause to lie exclusively in disturbances of the sexual glands. 4. Krabbe [23] believed that the tendency toward masculinization occurs in both sexes because the tumor develops from sexual glands of the masculine type, which, early in the embryo, become involved in the suprarenal cortex.

### PATHOLOGY OF TUMORS OF THE SUPRARENAL GLAND

Ewing [24] gave the following classification of tumors of the suprarenal gland:

Medullary:

- (*a*) Focal hyperplasia of
  - (1) Glial tissue or
  - (2) Chromaffin cells
- (*b*) Neuroma ganglionare
- (*c*) Neurocytoma, "sarcoma"
- (*d*) Suprarenal chromatophoroma

Cortical:

- (*a*) Hyperplasia, nodular or diffuse
- (*b*) Adenoma
- (*c*) Carcinoma

Of the medullary types, the neurocytoma has attracted most attention, as it has been observed more frequently than the other types, and because of its probable identity with congenital sarcomas and lymphosarcomas of the suprarenal gland as well as with retroperitoneal round cell sarcomas in infants and many embryonal growths of the cervical,

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20. Bulloch and Sequeira: On the Relation of the Suprarenal Capsules to the Sexual Organs, Tr. Path. Soc. London **66**:189, 1905.

21. Glynn, E.: A Comparison Between Ovarian "Hypernephroma" and Luteoma and Suprarenal Hypernephroma, with Comments on Suprarenal Virilism, J. Obst. & Gynæc. Brit. Emp. **28**:23, 1921; The Adrenal Cortex, Its Relation to Other Ductless Glands and Especially to Sex, Quart. J. Med. **5**:157 (Jan.) 1912.

22. Blanchard, R.: Le virilism et l'inversion des caractères sexuels sont sous la dépendance des glandes génitales interstitielles, Bull. Acad. de méd., Paris **76**: 47, 1916.

23. Krabbe, K. N.: The Relation Between the Adrenal Cortex and Sexual Development, New York M. J. **114**:4 (July 6) 1921.

24. Ewing, James: Tumors of the Adrenal, in Neoplastic Diseases; A Treatise on Tumors, Philadelphia, W. B. Saunders Company, 1928, p. 811.

thoracic and peripheral nervous system. The structure of these tumors varies with the degree of development of the nerve elements. According to Ewing, "the most immature types are perfect rosettes, very numerous, but ill-defined fibrils giving an abundance of hyalin stroma, or many hyalin globules staining with eosin. The hyalin globules resolve themselves into bundles of imperfect nerve fibrillae connecting groups of neurocytes. Various other structures may be interpreted as imperfect ganglion cells, axis cylinder processes, and glial fibers."

There are two well recognized clinical types of suprarenal neurocytoma. Hutchison [25] described a suprarenal sarcoma in infants with cranial metastasis. He reported 13 cases occurring in children from 3 months to 9 years of age. The metastasis may appear spontaneously or following trauma, with ecchymosis of the eyelids, soon followed by exophthalmos and a tumor of the orbit and temporal regions, with extensions to the regional lymph nodes. The orbital tumor may reach a large size, the primary abdominal focus being discovered only at autopsy. Other tumors besides those arising in the suprarenal gland may, of course, produce the same syndrome.

The second type is that described by Pepper [26] in which the prominence of hepatic metastases produces the striking clinical feature, with a rapidly enlarging abdominal tumor caused by growths in the suprarenal gland and liver. Frew [27] has shown by anatomic studies of lymphatic drainage why it is that tumors of the left suprarenal gland usually produce Hutchison's type of picture, whereas tumors of the right suprarenal gland follow the picture described by Pepper.

Vaquez [28] and others have noted high arterial tension with tumors of the suprarenal medulla, and epinephrine-like substances have been extracted from medullary tumors.

### TUMORS OF THE CORTEX

The simplest change in the cortex with neoplastic tendencies is hyperplasia. The hyperplasia may be nodular or diffuse. Both types are relatively rare. In the nodular form light yellow masses are seen, which vary in size from 1 mm. to 1 cm. in diameter. Diffuse hyperplasia may produce a syndrome of feminine pseudohermaphroditism.

25. Hutchison, R.: On Suprarenal Sarcoma in Children with Metastases in the Skull, Quart. J. Med. **1**:33, 1907-1908.

26. Pepper, W.: A Study of Congenital Sarcoma of the Liver and Adrenal with Report of a Case, Am. J. M. Sc. **121**:287, 1901.

27. Frew, R. S.: On Carcinoma Originating in the Suprarenal Medulla in Children, Quart. J. Med. **4**:123, 1910.

28. Vaquez, H.: Hypertension, Bull. et mém. Soc. méd. d. hôp. de Paris **21**: 120, 1904.

In structure, the areas of hyperplasia may resemble the normal zona glomerulosa or zona reticularis.

Adenoma of the suprarenal cortex is also infrequently encountered. Ewing found only 3 instances in a series of 1,500 autopsies. They may reach a large size, and the cells composing the adenoma may closely resemble those of the normal suprarenal cortex. More often they are smaller, more granular and free from fat.

Carcinoma of the suprarenal cortex may occur at any age, though in a series of 9 collected cases Rolleston and Marks [29] found the average age to be 44 years. The tumors, grossly, are soft and yellowish, with a marked tendency toward hemorrhage and necrosis. They are solid, though central softening may lend them a pseudocystic structure. Characteristics are the early and widespread metastases to distant organs, local extension to the kidneys and perirenal tissue and the infrequency of metastases to the bone.

Ewing described two forms of carcinoma of the suprarental cortex:

1. Adenocarcinoma, or adenoma malignum, resembles the adenoma described, with an orderly arrangement of cells reproducing the alveoli of the zona glomerulosa, or the anastomosing columns of the zona fasciculata. There are in addition, however, typical areas of a malignant character, and the tumor metastasizes. No diffuse growth of typical cells occurs. The atypical cells are large and the nuclei hyperchromatic.

2. Fully developed carcinoma presents several peculiarities of structure. There are numerous areas of large, granular, fatty cells in perivascular arrangement, resembling vascular adenocarcinoma. The cells are, however, more active, atypical and malignant. Giant cells are seen in varying proportions. In some tumors almost the entire growth seems composed of the giant cells. A type described by Ewing as carcinosarcoma consists of areas of alveolar or perivascular carcinomatous types of arrangement, interspersed with other areas in which are seen sheets of elongated, spindle-shaped, granular cells. Diffuse carcinoma is the most malignant form. Here the cells lose their resemblance to suprarenal parenchyma, and appear as rounded or polyhedral granular cells, notably free from fats and glycogen. They infiltrate surrounding tissues and produce bulky metastases.

*Incidence of Tumors of the Suprarenal Cortex.*—Carcinoma of the suprarenal cortex is a relatively infrequent form of tumor. In 1897, Williams [30] reported a single case in 8,378 tumors found in infants

29. Rolleston, H. D., and Marks, H. W. J.: Primary Malignant Disease of the Suprarenal Bodies, Am. J. M. Sc. **116**:383, 1898.

30. Williams, R.: The Malignant Tumors of Infancy, Childhood, and Youth, Lancet **1**:126, 1897.

and children. In 1899, Ramsay [31] was able to collect 57 cases of primary malignant tumors of the suprarenal gland as a whole, including medullary tumors. In the literature Gallais [1] found 51 cortical tumors with sexual alterations, all occurring in women and children. In analyzing 47,069 cases at the University of California Hospital, Gibson [32] found a total of 9 tumors of the suprarenal gland. Of these, only 4 proved to be primary suprarenal tumors, 2 being cortical and 1 medullary.

In 1925, Apert [2] was able to collect only 35 cases of cortical suprarenal tumor in which necropsy had been performed. In 1905, Bulloch and Sequeira [20] collected 12 cases of tumor of the suprarenal gland with sexual alterations. In 1928, Crosbie and Smith [33] described what they believed to be the nineteenth case of cortical suprarenal tumor, with typical changes in secondary sexual characteristics. Recently (1929) Fordyce and Evans [16] contributed 2 more cases of suprarenal virilism, one resulting from a carcinoma of the suprarenal cortex, the other from an operable, encapsulated tumor of the suprarenal cortex.

Though we made no attempt to collect every case that has been reported, we feel that the incidence of suprarenal tumors is sufficiently infrequent to justify the report of our case.

*The Relation of Cortical Suprarenal Tumors to Renal Hypernephromas.*—A review of the subject of suprarenal tumors would be incomplete without some mention of the present status of the relationship between suprarenal tumors and so-called renal hypernephromas.

The well known Grawitzian theory,[34] propounded in 1883, ascribes the occurrence of hypernephromas of the kidney to rests from the suprarenal cortex. This theory is supported by the embryonal proximity of the suprarenal cortex to the renal anlage and by the gross resemblance of hypernephromas to suprarenal carcinomas. Present opinion, however, is not in accord with Grawitz' theory. Glynn [21] excellently pointed out differences in the microscopic structure of the two tumors, and called attention to the fact that there is no association of renal hypernephroma with changes in sexual characteristics. A possible exception to this statement is found in the case reported by Richards,[35] in which, however, the growth in the kidney was bilateral

31. Ramsay, O.: A Study of Fifty-Seven Cases of Primary Malignant Tumors of the Suprarenal Glands, Bull. Johns Hopkins Hosp. **10**:20, 1899.

32. Gibson, T. E.: Diagnosis of Adrenal Tumors, with Classification of Adrenal Tumor Syndromes, and Report of Cases, J. Urol. **18**:33 (July) 1927.

33. Crosbie, A. H., and Smith, L. W.: Primary Tumors of Suprarenal Capsule with Especial Reference to Adrenal Virilism, Tr. Am. A. Genito-Urin. Surgeons **20**:179, 1927.

34. Grawitz, P.: Ueber Entwicklung der Nierentumoren, Deutsche med. Wchnschr. **10**:719, 1884.

35. Richards, Owen: Growths of the Kidney and Adrenals, Guy's Hosp. Rep. **59**:217, 1904.

and might well have been metastatic from an unrecognized primary focus in the suprarenal gland. Supporters of the Grawitzian hypothesis have yet to explain why suprarenal rests, though comparatively uncommon in the kidney, produce such a common tumor as hypernephroma—by far the commonest renal tumor—while suprarenal rests in other organs, though common, rarely produce tumors, benign or malignant. In 1,500 autopsies reviewed by Glynn, only 2 cases of nodules resembling suprarenal rests were found in the kidneys, both of these being papillary cystadenomas. Kelly [36] and Manasse [37] in their large series of autopsies did not give a single example of renal suprarenal rests.

As opposed to the infrequence of suprarenal rests in the kidney, the following data are illustrative of the comparative frequency of suprarenal rests in other organs. Wiesel [38] found suprarenal rests in the epididymis in 76 per cent of new-born males. Schmorl [39] found suprarenal rests in 4 of 510 livers examined at autopsy. Aichel [40] found rests in the broad ligaments and spermatic veins of twenty-four females. In these rests hyperplasia and adenoma is an extremely rare occurrence, and in 5 cases of Grawitzian tumors of the ovary reported by Vouviller,[41] none exhibited unusual sexual changes, all resembling renal hypernephromas rather than suprarenal carcinomas.

This evidence, though not conclusive, points strongly to the fact that renal hypernephroma bears no more than an accidental structural relationship to suprarenal carcinoma.

## PROGNOSIS AND TREATMENT

The prognosis of tumors of the suprarenal depends, as does that of neoplasms elsewhere in the body, on the character of the growth, the degree to which it has infiltrated adjacent structures and the extensiveness and accessibility of its metastases. Gibson [32] pointed to pyelography as a method of recognition of suprarenal tumor or confirmation

36. Kelly, A.: Ueber Hypernephrome der Niere, Beitr. z. path. Anat. u. z. allg. Path. **23**:280, 1898.

37. Manasse, Paul: Ueber die hyperplastischen Tumoren der Nebennieren, Virchows Arch. f. path. Anat. **133**:311, 1893.

38. Wiesel, Josef: Accessorische Nebennieren im Bereiche des Nebenbodens, Wien. klin. Wchnschr. **11**:443, 1898.

39. Schmorl, Georg: Zur Kenntnis der accessorischen Nebennieren, Beitr. z. path. Anat. u. z. allg. Path. **9**:523, 1891.

40. Aichel, Otto: Zur Kenntnis der Nebennieren, München. med. Wchnschr. **47**:1228, 1900.

41. Vouviller, Paul: Grawitz'sche Nebennieren Geschwulst des Ovariums, Beitr. z. path. Anat. u. z. allg. Path. **50**:161, 1911.

of its diagnosis. He called attention to the fact that the upper calices are compressed and the entire kidney pushed downward.

In at least 3 cases, successful removal of the tumor has been effected, with complete reversion of sexual characteristics to normal. Mauclaire,[42] Collett [43] and Holmes [6] reported cases in which operation had been successful. Holmes' patient was a young woman, with a large, slowly growing neoplasm of the right suprarenal cortex which Glynn, who examined it, believed to be benign. Collett's case was that of a girl 1½ years of age, and is probably the only one on record of the removal of an unquestionably malignant tumor of the suprarenal cortex with complete recovery. Crosbie and Smith [33] recently reported a case in a woman, 38 years of age, in whom a cortical suprarenal adenoma with cystic degeneration and hemorrhage was removed, with apparent reversion of the secondary sexual changes, consisting of enlargement of the clitoris and hirsutism.

55 East Washington Street.

42. Mauclaire, P.: Tumeur de la conche corticale de la capsule surrénale droite observée chez une femme et ayant provoqué l'habitus masculin, Bull. et mém. Soc. de chir. de Paris **46**:796, 1920.

43. Collett, Arthur: Genito-Suprarenal Syndrome (Suprarenal Virilism) in a Girl One and a Half Years Old, with Successful Operation, Am. J. Dis. Child. **27**:204 (March) 1924.

# TUMORS OF THE HEART AND PERICARDIUM

## PATHOLOGY, SYMPTOMATOLOGY AND REPORT OF NINE CASES*

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Tumors of the heart and pericardium, both primary and secondary, are rare. Most of them are asymptomatic and are, therefore, of interest only to the pathologist. Some, however, are the cause of cardiac dysfunction or even failure, and are thus of some concern to the clinician. Only once has a primary tumor of the heart been diagnosed during life and only a few times, a metastatic lesion. A review of the clinical history of some of the cases on record shows that occasionally a neoplasm might have been suspected had the clinician borne this possibility in mind. There is something intensely satisfying in diagnosing correctly a rare lesion, and it is hoped that this article will impress its readers so that they will be on the alert to recognize the condition should it happen to come under their observation. I shall attempt a comprehensive but not complete review of the subject and shall add several cases to the literature.

### SECONDARY TUMORS OF THE HEART

Secondary tumors of the heart are perhaps somewhat less rare than the primary neoplasms. There are four interesting questions that might be asked that apply to metastatic growths in the heart, two of which (1 and 4) are applicable also to certain types of primary growths: 1. Why are neoplasms so uncommon in the heart? 2. Why do metastatic lesions have such a predilection for the right side of the heart? 3. Why are the valves practically never involved in secondary growths? 4. Why do such massive growths occur with extensive destruction and replacement of myocardium or with mechanical embarrassment, and yet produce in many instances so little disturbance of cardiac function?

As regards the first question, the heart is probably unfavorable for implantation because of its active contraction (Jägers). Adami said:

> The heart above all organs is constantly in a state of great efficiency, well nourished, well innervated and functionally always active, so that it is less likely to take on aberrant growth.

Karrenstein gave the incidence of cardiac metastases as 7.5 per cent in cases of disseminated growths. He cited the following statistics:

* Submitted for publication, Jan. 12, 1931.
* From the Georgetown University School of Medicine.

In 2,161 autopsies, Chambers found 7 secondary carcinomas of the heart; from 4,547 autopsies, Willigk reported 9 secondary carcinomas of the heart, 7 of which were in the pericardium; in 4,500 autopsies, Uskoff found 1 secondary carcinoma of the heart; in about 8,500 autopsies, Napp saw 3 secondary carcinomas of the heart; at the Roth Institute of the University of Berlin (Karrenstein), among 6,655 autopsies there were 15 carcinomas (8 of which were pericardial) and 4 secondary sarcomas of the pericardium. Peters and Milne gave more statistics: Blumensohn reported that of 1,078 cases of disseminated carcinoma, the heart was involved in 34, and of 160 cases of sarcoma, in 12; Pic and Bret found 25 metastatic carcinomas of the heart in 1,708 autopsies; Thorel found 15 in 3,000 autopsies, and Ely 7 in 2,161 autopsies. At the Russell Sage Institute of New York there were 3 cancers of the heart in 1,976 autopsies; at the Johns Hopkins Hospital up to the year of 1907, there were 10 tumors of the heart in 2,942 autopsies, all secondary except a rhabdomyoma. At the Stanford Medical School, Morris reported 2 carcinomas and 3 sarcomas in 3,000 autopsies.

Metastases to the heart have occurred from neoplasms of all of the main organs:

Cancer of the trachea (Linell)
Cancer of the tongue (Lisa) (Geipel)
Cancer of the stomach (Peters and Milne) (Widal and Abrami) (Geipel) (Moore)
Sarcoma of the kidney (Moore) (Rabé and Morel)
Cancer of the submaxillary gland (Wagner)
Rodent ulcer of the face (Pic and Bret)
Cancer of the esophagus (Moore) (Geipel, six cases)
Cancer of the rectum (Peters and Milne) (Thorel)
Lymphosarcoma (Peters and Milne) (Aubertin) (Morris) (Windholz) (Napp)
Cancer of the pancreas (Barthélémy)
Cancer of the breast (Hektoen) (Kapsinow) (Goldstein) (Ehrenberg) (Geipel)
Sarcoma of bone (Hektoen) (Goldstein) (Allyn and Karsner) (Morris) (Laplace and Karsner) (Tedeschi) (Bardenheuer) (Willius and Amberg)
Sarcoma of the eye (Goldstein)
Pigmented soft mole of labium majus (Goldstein)
Cancer of the uterus (Geipel, two cases) (Rist and Rolland) (Thorel, two cases)
Cancer of the lung (Caussade, Surmont and Lacapére) (Bosco) (Morris) (Windholz)
Cancer of the testis (Kanthack)
Hypernephroma (Patzdorf) (Polayes and Taft)
Sarcoma of the skin (Allyn and Karsner)
Sarcoma of the pleura (Pommay-Michaux and Boué)
Sarcoma of the nose (Warthin)
Cancer of the bronchus (Geipel) (Morris) (Fishberg, two cases)

Cancer of the clitoris (Arnold)
Sarcoma of the uterus (Thorel)
Cancer of the gallbladder (Thorel)
Cancer of the kidney (Thorel)
Cancer of the vulva (Geipel)
Cancer of the ovary (Geipel)
Cancer of the liver (Geipel)
Epidermoid carcinoma of the scalp (Campagna, Maurice and Hauser)
Metastases to the heart from a primary tumor of the heart itself, usually sarcoma, also occur.

There are three types of secondary invasion of the heart. Secondary invasion occurs most commonly as part of general dissemination; next in order of frequency, as a more or less solitary metastasis from a nearby organ and least often by direct extension from an adjacent organ.

In the majority of cases in which metastasis has occurred, the transmission has been considered as having been made through the blood. Tumor cells have been found in circulating blood, in thrombi (Peters and Milne, and Menetrier), as vegetations on the endocardium and as strands of cells loose in the coronary vessels (Moore); huge masses of tumor tissue have been found filling the venae cavae and the right side of the heart, as in the case of Carnot and Lambling of sarcoma of the stomach and as in case 4 of this report of hypernephroma. Many cases are associated with primary or secondary intrathoracic neoplasms, from which the tumor cells may gain access to the left side of the heart through the pulmonary veins and thence to the coronary arteries and the cardiac muscle. In the less common cases of implantations on the endocardium of the right side of the heart, the tumor cells probably gain entrance to the blood stream from the lymphatic duct, and pass to the superior vena cava via the bronchial and azygos veins (Hektoen). From these grafts it may even be possible that emboli pass into the lungs and cause metastatic lesions there (cases of Delherm and Laignel-Lavastine, Rist and Rolland, and Warthin).

Probably a smaller number of metastases occur through the lymphatics. This would come about by retrograde conduction through the tracheobronchial lymph nodes, which drain the myocardium and pericardium as well as the pleura and lungs (cases of Aubertin and of Wolf and Giet).

In case of direct extension, the lymphatic canals may or may not play an important rôle. Strands of tumor cells invade the interstices of the surrounding tissues and by their mass destroy by pressure, or they follow fascial planes in the lines of least resistance. This mechanism is, of course, possible with primary tumors of the lung, bronchi, esophagus or mediastinum or from secondary involvement of intrathoracic lymph nodes. Two of Geipel's cases demonstrate different

modes of direct extension. In one, a carcinoma of the bronchi broke through into the upper left pulmonary vein and extended into the left auricle, while in the other a carcinoma of the esophagus forced itself through the wall of the left auricle. In one of Napp's cases, a medullary sarcoma of the posterior mediastinum grew into the muscle of the heart through the right auricle; in another, the left auricle was invaded, while in a third, not only was the right auricle invaded from above but metastatic nodules were found in the wall of the right ventricle. In a case reported by Morison a mediastinal sarcoma almost completely replaced the walls of both auricles and of the right ventricle and the apex of the left ventricle.

As to the types of secondary lesions and their size, shape and distribution there is the greatest variation. Carcinomatous metastases are more common than sarcomatous. The lesions are frequently similar to those found in other organs, viz., small, whitish, firm nodules, discretely or diffusely scattered throughout the myocardium. In other cases, more often of sarcoma, there may be a diffuse infiltration and replacement of the myocardium, sometimes with great thickening of the walls and encroachment on the cavity (case of Windholz). The nodules may be of large size and project internally, externally or both. The heart may or may not be enlarged and deformed, depending on the extent and nature of the involvement. The valves are rarely involved, although in the cases of Widal and Abrami, Rist and Rolland, and Kanthack large vegetations occurred from tumor cells engrafted on the valves, and the condition resembled vegetative endocarditis. Occasionally a large polypoid growth encroaches on the chamber of the heart (Pommay-Michauz and Boué); this may be pedunculated. In Warthin's case a metastatic nodule lay free in the cardiac cavity and acted as a ball valve. The secondary growth may rarely outstrip the primary growth. The pericardium may be involved by an infiltration, with thickening; often in such cases there is a fibrinous exudate on the two layers and a hemorrhagic or nonhemorrhagic effusion. In rare cases the superficial lymph vessels of the heart and pericardium are involved in a carcinomatous lymphangitis and stand out as whitish threads (Aubertin). The histologic structure of the primary tumor is usually reproduced. With the sarcomas there is often an infiltration of cells between the muscle fibers of the myocardium, causing atrophy of the fibers. Leukemic infiltrations may produce, besides diffuse infiltrations, definite nodules resembling tumor metastases (Cochineal and Jolly) (Willius and Amberg). Similarly, animal parasites such as Cysticercus, may cause tumor-like nodules in the heart, echinococcus cysts and hydatids (Mönckeberg).

The location of the lesions may be anywhere, but the right side of the heart, especially the ventricle, seems to be favored. The lesions are intramural, subendocardial, subepicardial, septal, auricular, ventricular, etc. The orifices are seldom encroached on to a serious extent. Involvement of the conduction system may produce heart block.

Why the right side of the heart should be more commonly or more extensively involved than the left is rather well explained, as Windholz pointed out, by the work of Kretz. Since studies of the lymphatic system do not seem to explain the predilection, Kretz, using the method of Crainicianu, injected a solution through the coronary arteries constantly for five minutes at a pressure of 130 mg. of mercury and measured the fluid escaping from the coronary veins and the cavities of the heart. He found that one fifth of the fluid escaped through the coronary veins while four fifths was lost into the chambers; of the fluid in the chambers, one fourth was lost in the left and three fourths in the right side of the heart. Of the fluid passing out through the coronary veins, one fifth went from the left and four fifths from the right. Kretz explained that the fluid passing directly into the cavities of the heart passed from the coronary arteries to the venae minimae thebesii, and by injecting a colored medium he demonstrated this route. Thus the reason for the preference of tumor cells for the right side of the heart may be explained on a blood-vascular basis. The freedom of the valves from involvement, except rarely by implantation, is explicable likewise on a circulatory basis, the valves being relatively avascular.

Concerning the possible reasons for the frequent lack of serious cardiac dysfunction in the presence of extensive neoplastic involvement of the heart, both from primary and secondary growths, Geipel assumed that the slow development of the growth may give time for compensatory changes, while Bardenheuer expressed the opinion that it is due mainly to freedom of the valves from invasion. These reasons hardly seem sufficient when one considers the following cases, in which cardiac symptoms were either lacking or of minor nature or practically terminal in occurrence. Grawitz' case of thymic lymphosarcoma spread into the superior vena cava and formed an envelope about the left auricle from 1 to 2 cm. thick, while the entire right ventricle was practically sarcomatous. In Morison's case of mediastinal sarcoma there was practically no ventricular myocardium left. Metastases from a gastric carcinoma so completely involved the heart (Napp) that only a part of the myocardium at the apex was left, and the chamber of the left ventricle was merely a cleft. In Ehrenberg's case a metastatic tumor the size of a fist enveloped the heart, and the left ventricle appeared as a small appendage thereto. Windholz recorded a mediastinal sarcoma

so involving the heart secondarily that only the anterior surface of the left ventricle was free.

The symptomatology from a clinical point of view will be considered under a separate heading.

## PRIMARY TUMORS OF THE HEART

Primary tumors of the heart are more interesting than secondary, and have been the source of much discussion. More than 150 cases have been reported in the literature. There are a number of kinds of primary tumors that occur in the heart: myxoma, sarcoma, rhabdomyoma, fibroma, lipoma, endothelioma, varix, hemangioma, lymphangioendothelioma and leiomyoma. Most of the tumors described have been benign, about 20 per cent being malignant. Of 143 cases of primary neoplasms of the heart collected by Mendelstamm (1923), 117 were benign and 26 malignant. The benign tumors were mainly myxomas, the malignant, almost entirely sarcomas. Mendelstamm gave their distribution as follows:

| | Right Auricle | Right Ventricle | Left Auricle | Left Ventricle | Both Auricles and Auricular Septum | Both Ventricles and Ventricular Septum | Multiple Sites | Valves |
|---|---|---|---|---|---|---|---|---|
| Benign | 9 | 8 | 44 | 23 | 6 | 5 | 8 | 17 |
| Malignant | 11 | 1 | 2 | 2 | 2 | 2 | 2 | 4 |

Of the valvular tumors, the locations were as follows:

| | Mitral | Aortic | Tricuspid | Pulmonic |
|---|---|---|---|---|
| Benign | 2 | 3 | 5 | 4 |
| Malignant | 1 | 1 | 1 | 1 |

For sex distribution, Mendelstamm gave:

| | Male | Female |
|---|---|---|
| Benign | 57 | 33 |
| Malignant | 15 | 8 |

For age distribution, he divided the cases as follows:

| | Up to 20 Yrs. | 20-40 | 40-60 | Over 60 |
|---|---|---|---|---|
| Benign | 31 | 17 | 29 | 21 |
| Malignant | 2 | 9 | 8 | 3 |

### MYXOMA

Myxoma is the most debated type of tumor in the heart. Ribbert was inclined to think that most of the tumors described as myxoma or a variety of myxoma are true neoplasms, while others, like Thorel, Stahr, Karrenstein and Husten, expressed the belief that these tumors are thrombi swollen by imbibition of plasma and in various stages of organization. The latter contended that myxomatous changes may

occur in these edematous thrombi. Thus, of 71 cases described in the literature as endocardial myxomas, Husten, in 1923, after critical analysis, accepted only 9 as true myxomas. One could accept by the same standard 5 other cases reviewed by Mendelstamm (Wigand, Meyer, Hlava, Nowicki [2]), making thus only 14 myxomas. Husten admitted that the differentiation was difficult. Ribbert, on the other hand, claimed that there is no difficulty in the distinction. It appears that most men continue to call these questionable formations myxomas. Altogether about 75 cases of myxoma arising from the mural endocardium have been described.

Myxomas range in size upward from that of a pea, often becoming as large as a hen's egg or a medium sized apple. They may be smooth and rounded, lumpy or polypoid and villose. The surface is smooth and glistening, as a rule, and the appearance gelatinous. They are usually pale yellow, bluish gray or yellowish brown, often with hemorrhagic areas on the surface, and sometimes partly covered with fibrin; the consistency is more or less elastic. On cut section they are gelatinous and often hemorrhagic. They are usually attached by a short stalk, and are entirely intracavitary. Microscopically, the tumor is seen to be covered with the normal endothelium of the endocardium. The groundwork is an amorphous, finely granular or finely fibrillar material which may or may not stain as mucin. Cells of different varieties are seen, varying in number in different cases and in different parts of the same tumor; often they are relatively few compared to the amount of tumor tissue. In many there are large stellate cells typical of mucoid tissue. In some there are also cells that are large and multinucleated, others that are fusiform; inflammatory elements, such as lymphocytes and plasma cells, are often seen. Blood vessels are usually present, numerous in some cases, but often scanty, usually of a delicate structure, and appearing as mere capillaries with endothelial walls. Small hemorrhages and scattered erythrocytes are commonly present, together with pigments consisting of hemosiderin and hematoidin. Connective tissue fibers and often elastic fibers are found. Some of the tumors grossly resemble primary sarcomas of the heart, and really differ essentially only in the predominating type of cell and in their greater cellularity.

Myxomas arise from the endocardium, usually of the chambers and more often of the left auricle in the region of the fossa ovalis, but sometimes from the valves. Most of the small nodules arising from the valves, however, are either greatly modified myxomas or fibromas, endotheliomas, and other tumors.

It seems to me that the argument concerning the nature of these myxomatous masses is all in favor of their neoplastic origin. Ribbert

has been the champion of this view. He maintained that the masses are usually too large to be organized thrombi. Everywhere else in the body thrombi have a tendency to retract and become almost completely effaced. It is difficult to conceive of thrombi forming in otherwise normal hearts not showing the slightest evidence of a previous endocarditis or trauma, as many of the tumors do. These tumors occur almost exclusively in the auricles, whereas thrombi occur just as frequently if not more so in the ventricles. There appears to be an entire absence of stages intermediate between definite thrombi or endocardial vegetations and these myxomatous masses. Ribbert contended that rests of embryonic mucoid tissue in the heart undoubtedly persist at times, especially in the rim of the foramen ovale. Such tumors as these differ from embryonic tissue in that there is a relative increase of mucin. Ribbert explained the fact that the valvular tumors often approach the fibroma because the mucoid tissue originally forming it has become fully formed fibrous tissue, which is the ultimate developmental intention of mucoid tissues. There seems to have been considerable contention concerning the point as to the exclusiveness of mucin in myxomas. Ribbert and Leonhardt maintained that true mucin occurs only in genuine blastomas. Djewitzky, Koniger and Honegger, however, found mucin in undoubted thrombi or thickenings of the endocardium. Too much stress is apparently placed on the presence or absence of mucin. Prolonged fixation in formaldehyde may prevent the staining reaction, or the stains may be untrustworthy. Nowicki considered his case 2 true myxoma, although the mucin reaction to thionin was not obtainable, and star cells were not present. Stahr maintained that myxomas are distinguished from organized thrombi by their poverty of cells. The presence of star cells certainly points toward myxoma, and in true myxomas round and spindle-shaped cells are also observed. The presence of hemorrhages is easily explained by the delicate structure of the vessels and the mechanical conditions to which the tumor is subjected. Lymphocytes and plasma cells always occur in such regions. All tumors may contain hemosiderin. In organized thrombi, hemosiderin is found at the periphery and hematoidin in the center, whereas in these tumors hemosiderin is found scattered throughout. In thrombi, one expects the organization to occur from the periphery and the connective tissue on top of this, but Meroz found a neoformation of capillary vessels in a myxoma in the midst of the fundamental substance in fully organized tissue. One expects stratification in an organized thrombus, but no evidence of stratification is present in these tumors. The presence of elastic fibers is without meaning since they are also present in thrombi; but in these tumors they are more or less peripheral and probably derived from the subendocardium. The presence of elastic tissue has lead some observers to give a modified name to the tumor, as Kerrenstein

with his elastomyxoma and Askanazy with his fibro-elastomyxoma. Sometimes the vessels in the tumor show a greater development than is usual in thrombi. Likewise against thrombi is the fact that the vessels and cells of the outer and inner parts are similar. Owing to the vascularity and presence of fibrous tissue, Fabris and Csemes designated their cases as fibro-angiomyxoma. Brenner called his an hemangio-elastomyxoma. The lobulated, villose or aciniform structure of many of the tumors speaks more for the true tumor, but Nowicki did not think that the smooth surface of his two large myxomas was against their neoplastic origin. Finally, as Bohrod pointed out, in spite of the rarity of all tumors of the heart, primary sarcomas originating in the endocardium do occur, and wherever there are malignant mesenchymal tumors, benign tumors may also occur.

Many of these myxomas are unusually interesting because of their size, situation and pedunculated nature which allows them to plug up an orifice of the heart, usually the mitral. The clinical features will be considered later.

### FIBROMA

Fibroma is considered next because it is an endocardial tumor and is assumed to be of a similar nature to myxoma. The fibromas arise from the subendothelium of the valves. They are usually single, never larger than a cherry, are papillary and pedunculated. About 25 cases of this type have been reported; all were similar. Nine were located on the tricuspid valve, 6 on the aortic, 5 on the mitral and 5 on the pulmonary. In only 4 cases was there evidence of chronic endocarditis. The cases group themselves into those without and those with an organized system of blood vessels. A few of them closely resemble the mural myxomas previously described; others are similar to the cases reported hereafter by me, avascular, hyaline and sparsely cellular; while others are atypical and difficult to classify, such as the endothelioma of the mitral valve of Forel and the hemangiofibroma of the pulmonary valve of Bohrod. Whether both of these should be grouped here under fibroma is questionable, but they seem to be of the same general nature as the others in this group. At least they are all benign tumors of the cardiac valves.

The main conceptions of the nature of these tumors are that they are all really myxomas, that they are organized thrombi, that they are similar to Lambl's excrescences and that they are connective tissue tumors undergoing various degenerations. Many of the same objections given in the discussion on the myxoma against the thrombus theory of origin apply again, the important ones here being the highly developed papillary nature of the growth, the homogeneous structure and the absence of pigment or other signs found in organizing thrombi. A few

words regarding the theory, first of Koechlin and later of Thorel, that they are similar to Lambl's excrescences might be appropriate. These threadlike processes arising usually on the nodulus arantii or annulus of the aortic valve and rarely from other valves were first described by Lambl in 1856. They are quite common, occurring in about 20 per cent of hearts. They are composed of lamellated hyaline connective tissue with a well defined axis cylinder and are covered by endothelium; they are practically without nuclei but have numerous elastic fibers. It seems strange, however, that intermediate forms do not occur and that while the excrescences are common the papillomas are rare; likewise, practically all of Lambl's excrescences are situated, as Dean and Falconer pointed out, on the aortic valve, while only 8 of 27 fibromas (including the cases reported here) were on this valve. When one considers the highly papillary structure, the smooth, shining surface and the fact that the growth occurs usually on a normal valve, the idea of a connective tissue tumor seems logical. If Ribbert's assumption is correct, that mucoid tissue ends developmentally as connective tissue, then one may consider these growths also as myxomas, which some of them closely resemble.

Intramural fibromas, fibroids or chancroids, have been described in earlier years, but it is somewhat questionable if the 2 main cases, those of Luschka and of Albers, were actually of this nature. Mönckeberg mentioned a case of fibroma of the ventricular septum described by Wagstaffe. These tumors do not produce clinical symptoms or functional disturbance, all being innocent postmortem discoveries.

### SARCOMA

Perlstein, reviewing this type of primary cardiac tumor in 1918 and adding a case of primary sarcoma of the pericardium, found only 31 (including his) recorded cases of primary sarcoma of the pericardium or heart. Since then, at least 15 more have been recorded (Göttel, Goldstein, Gödel [2], Rose, Mandelstamm, Pinault, Williams, Kohlenberger, Beck and Thatcher, Nowicki, Matras, Müller, Hill, Diebold).[1] Of 45 of these 46 tumors, 15 were spindle cell sarcoma, 14 round cell (small or medium size), 4 giant cell, 3 myxosarcoma, 3 fibrosarcoma, 4 mixed cell, 1 angiosarcoma and 1 lymphosarcoma. The apparent seat of the original tumor in these cases was:

| | |
|---|---|
| Right auricle | 18 |
| Left auricle | 9 |
| Pericardium (2 from subepicardial tissues) | 10 |
| Right ventricle | 2 |
| Right and left auricles | 1 |
| Left ventricle and auricle | 1 |
| Ventricular septum | 1 |
| Aortic valve | 1 |
| Pulmonary valve | 1 |
| Left ventricle and both auricles | 1 |
| Diffuse | 1 |

1. Not including the "rhabdomyosarcoma" of Bradley and Maxwell.

Thus it is seen that the majority of sarcomas of the heart arise from the auricles (preferably the right, and often the interauricular septum) and the pericardium. It is interesting to recall that most of the myxomas arise from the auricles, preferably the left, and often the interauricular septum. Grossly, some of them resemble certain of the sarcomas. Why the malignant growths should preferably arise in the right auricle and the benign in the left is impossible to answer. Metastases occurred in 21 cases as follows:

| | |
|---|---|
| Lung | 5 |
| Liver | 2 |
| Pancreas | 2 |
| Suprarenals | 2 |
| Mediastinal lymph nodes | 2 |
| Mediastinal lymph nodes and pleura | 1 |
| Tracheal lymph nodes and suprarenals | 1 |
| Lung and pararenal tissue | 1 |
| Lungs, pleura and brain | 1 |
| Lungs and pancreas | 1 |
| Kidneys | 1 |
| Tracheobronchial and mediastinal lymph nodes, pancreas and kidneys | 1 |
| Pleura, subcutaneous tissue and peritoneum | 1 |

In 16 cases there was hydrothorax, the fluid being bloody in 6. Pericardial effusion was found in 15 cases, in 10 of which it was bloody. In 7 instances the pericardium was partly or entirely obliterated.

The size of the tumors varies from that of a walnut to that of a child's head. The growth may be intracavitary, intramural, pericardial or mixed. Anatomically, one may also roughly classify the sarcomas into two other groups; those more or less sharply circumscribed and those without sharp limits and rather diffusely involving the heart, sometimes growing over the corona of the heart or invading extensively the mediastinum. Most of the intracavitary tumors fill the auricle in which they have originated. In Baldwin's case a pedunculated tumor, 5 by 6 by 7 cm., lay in the left auricle, being attached by a peduncle to the region of the mouths of the pulmonary veins. In Binder's case a pedunculated tumor the size of a walnut hung down from the right auricle into the mouth of the vena cava, nearly filling the right auricle. Bodenheimer's sarcoma consisted of about twenty nodules on the anterior surface of both auricles, growing into the cavity of the right auricle. In the case of Broadbent, the pericardium was from 0.5 to 1.5 cm. thick. In Schöppler's case, the entire pericardium was involved. Crescenti described a sarcoma located intramurally in the ventricular septum in a patient, aged 3 years, who died of scarlet fever. In some cases, as Lambert's, the pericardium was the origin of a growth which extensively infiltrated the myocardium. In Fuhrman's first case, the tumor resembled a bunch of grapes growing on the aortic valve and obliterating the mouth of the right coronary artery, while the left coronary artery was occluded by a plug of tumor tissue (the patient died suddenly without previous symptoms). In Mandelstamm's interesting case, two of the pulmonary valves were involved in two tumor

masses, one the size of a walnut, which almost completely obstructed the mouth of the pulmonary artery; there were large metastatic nodules in both lungs. The tumor in Perlstein's case originated from the subepicardial connective tissue and formed a large intrapericardial cystic tumor on the right, posterior and diaphragmatic surfaces of the heart, measuring 13 by 8 by 5 cm. Redtenbacher's angiosarcoma of the pericardium contained a cavity communicating with the right ventricle. The fibrosarcoma described by Raw had extended continuously from the right auricle through the inferior vena cava to the under surface of the liver. Weiss recorded a tumor the size of a child's head, involving mainly the right auricle, which had broken through the interauricular septum, infiltrated extensively the myocardium and almost completely enveloped the heart. The case of Beck and Thatcher was similar; there were extensive metastases in the pleura, peritoneum and subcutaneous tissue from a sarcomatous thrombus in the left auricle. The case of Williams is unusual in that only the parietal pericardium was involved. From these examples, it is seen that the sarcomas arising in the heart or pericardium are extremely variable in their characteristics and not infrequently malignant.

Sarcomas of the heart may occur at any age, having been found anywhere from the age of 3 to 79 years, most of them coming between 18 and 58 years. They predominate in males, in the proportion of twenty-five to sixteen. The apparent duration of the tumor is from one month to three and one-half years.

Here again, as in secondary tumors, it is difficult sometimes to conceive how the neoplasm can become so extensive and the heart continue to function. In the case of Matras, for instance, one is amazed at the great anatomic involvement of the heart and the brevity of the clinical course and meagerness of the cardiac signs.

The clinical features will be discussed separately.

### RHABDOMYOMA

Of all of the primary tumors of the heart the rhabdomyoma is perhaps the most interesting. From the time von Recklinghausen described the first case, in 1863, until Seiffert, in 1900, carefully studied these tumors, there had been much discussion regarding the situation of the large vacuoles seen in the tumor. To the satisfaction of all, Seiffert showed that these vacuoles were within the cell bodies of large embryonic fibers of the cardiac muscle whose sarcoplasmic body had continued to grow without, however, any additional differentiation into the adult type of cell. Normally, these embryonic myocardial fibers develop fibrils at the expense of the vacuoles, so that the fully mature muscle fiber is a solid, compactly fibrillar, cross-striated structure. By means of Best's

carmine Abrischoff demonstrated glycogen granules in the vacuoles of these embryonic muscle fibers. The "spider cells" of earlier writers, originally thought to be connective tissue cells, were shown to be the nuclei of these embryonic muscle fibers suspended in the vacuoles by a network of fibrils from the sarcoplasmic portion of the cell body.

Another thought which had to be exploded was that these large cells, which in many respects resemble Purkinje fibers, were in fact derived from these cells. By showing the absence of any anatomic connection with the elements of the conduction system, Bundschuh, Amersbach and Handorn and others demonstrated conclusively that this theory was wrong. Bundschuh considered that these tumors had already originated in the common mother tissue of the two muscle systems of the heart before their differentiation had occurred; this conception is strengthened by the relatively frequently observed fact that the rhabdomyoma fibers may show a transition into the myocardial fibers at the edges of the tumor.

Much discussion has arisen likewise concerning the nature of these tumors, whether they represent secondary growths from simple rests of embryonic tissue or a generalized disturbance of tissue differentiation. Steinbiss championed the view, based largely on the frequent association of similar malformations in other organs, that these rhabdomyomas are phenomena of a general developmental disturbance due to an abnormal germ condition, and that they have nothing to do with the germ explosions conditioned by mechanical developmental disturbances as conceived by Ribbert. According to Steinbiss, the tumor cells preserve morphologically the embryonal type, but reach a high degree of tissue maturity. This is shown not only by the gigantic size which the tumor cells attain but by regressive changes that are often observed, such as the replacement of connective tissue and sometimes even calcification. All cases appear to have reached their final development in embryonic life, appearing the same whatever the age of the patient. The tumor cells do not increase in number of elements but the single elements may hypertrophy, the sarcolemma increasing to a much greater degree than the myofibrils or contractile elements.

Microscopically then, as indicated, the rhabdomyoma of the heart consists of tubular muscle cells which often have a diameter many times that of normal fibers; where it is thicker and fibrillar, the wall of the tubes shows decided cross striations. In the large central vacuoles or lumens there are nuclei, appearing like spiders in a web, arranged in series at certain distances, and other nuclei are seen in the periphery. In their content of connective tissue, cases differ much, but usually the amount is small. The impression is often given that the tumor elements form a syncytium due to the peripheral fibrils

crossing from one tube to another in the absence either of distinct cell boundaries or uniformity in direction of the long axis; fat is not uncommonly found within the tumor elements. In a case reported by Bundschuh a nodule near the apex of the heart contained both myomatous and lipomatous portions without a sharp line of demarcation. The cases of Tedeschi and Spälty were somewhat similar.

At least 41 cases of rhabdomyoma of the heart have been recorded in man and reports have appeared of instances in the lower animals. The human cases were collected by Farber (1931). In general, there are three morphologic types of rhabdomyoma: (1) solitary, (2) multiple and (3) diffuse. The solitary nodule is usually located at the apex of the heart and is unassociated with other developmental abnormalities. The multiple nodules may be subendocardial, intramural or subepicardial, and may or may not project into the cavities of the heart or the pericardial sac. They show frequent transitions to normal cardiac muscle and are often associated with other developmental conditions, particularly tuberous sclerosis of the brain, mixed cell tumors of the kidneys and adenoma sebaceum of the skin. The patient may or may not be feebleminded or epileptic. In the diffuse variety (cases of Ribbert and Uehlinger), the rhabdomyomatous elements occur as small circumscribed nodules and are also scattered through the cardiac muscle without definite grouping. In Schmincke's case, all of the myocardium was composed of rhabdomyoma fibers; the patient was a new-born infant and the heart was twice normal size but not malformed.

The age incidence of death of persons with rhabdomyoma is: newborn, 4; first year, 14; second year, 5; third year, 5, and 1 each in the fourth, fifth, sixth, seventh, eighth, tenth, fourteenth, sixteenth, twentieth, twenty-first, thirty-first, and thirty-fifth years. Whether death occurs because of the rhabdomyoma depends, of course, on the extent of involvement of the heart, the size of the nodules and the position of large nodules. In the patients of Steinbiss dying at 21 and 35 years of age there were only one or two small nodules and no circulatory embarrassment. When the growth is large and at the apex, in the left ventricle or septum, or obstructing an orifice, such as the pulmonary in Ponfick's case, death occurs early. Strangely, in Uehlinger's case of diffuse involvement there was no circulatory embarrassment, the patient dying of tetanus at the age of 20 years.

### MISCELLANEOUS TUMORS

Other primary tumors of the heart have been recorded but are rare even compared to those already described. These are the lipoma, lymphangio-endothelioma, hemangio-endothelioma, leiomyoma and rhabdomyosarcoma.

According to Martin, about 21 cases of lipoma have been recorded. The summary of Verliac and Morel, in 1909, gave 11 previously reported cases, to which they added 1. Besides 4 other possible cases concerning which Verliac and Morel could not obtain accurate data, Mönckeberg mentioned 3 more by Handfort and another by Dittrich. Thorel claimed 1 for Kirch-Hertel and 1 for Pommer, and Martin described a further case. The lipomas are usually small but may become as large as a hen's egg. They are often subepicardial or subendocardial, but may be intramural. Those that are subepicardial are rather large, flat, smooth, whitish yellow and usually pedunculated. Those that are subendocardial are not as large and are usually sessile. In the case reported by Brewis, the tumor was attached by a pedicle on the interventricular septum, and completely obstructed the tricuspid orifice. In the cases reported by Spälty and Tedeschi, the lipoma was surrounded and penetrated by cardiac muscle fibers. Most of the patients were past middle age and did not have symptoms of cardiac dysfunction. Concerning the origin of the subendocardial lipomas, Thorel asserted that they are derived from those little, usually circumscribed, round or oval clusters of fatty tissue that are seen occasionally under the endocardium of the free wall of the right ventricle or of the septum and rarely of the left ventricle.

To my knowledge, only 3 instances of lymphangio-endothelioma have been described, 2 of which were extremely interesting because they caused complete heart block. The case reported by Armstrong and Mönckeberg (1911) was a small tumor, 8 by 6 by 5 mm., located in the region where the bundle of His emerges from the auriculoventricular node; it was interpreted as being derived from the lymph vessels of the node, with which it is richly supplied. This was stated to be the first blastomatous new growth of the specific muscle system reported in the literature. In the case of Lloyd (1929) the tumor was 15 by 12 by 8 mm., without a definite boundary, although quite sharply localized, situated in the region of the auriculoventricular node. The third case was recorded by Forel as a small discoid excrescence with smooth surface and soft consistency, about 2.5 mm. in diameter, with a pedicle, located on the auricular aspect of the posterior flap of the mitral valve.

A hemangio-endothelioma was described by Penneman on the anterior wall of the left auricle, about the size of a chestnut and projecting 1.5 cm. into the cavity of the auricle. A hemangioma cavernosum was described by Schuster on a papillary muscle of the right ventricle. This is similar to Rau's case of a cherry-sized cavernoma in the subendocardium of the right auricle and to Train's, of a tumor the

size of a hazelnut in the ventricular septum. Mönckeberg expressed the belief that tumors of the type of the latter three were not blastomas, but probably varices.

A malignant leiomyoma was described by Eschbach (1928) as originating from the wall of the pulmonary artery, involving the pulmonary valves and almost completely occluding the left pulmonary artery. There is some question as to the nature of this tumor; possibly it is a polymorphous cell sarcoma or a malignant endothelioma. The author's reasons for his diagnosis seem rather convincing, however. Nagayo described several minute fibromyomatous nodules within a large branch of the left bundle branch.

Bradley and Maxwell (1928) described a large tumor filling the pericardial cavity and invading the cardiac muscle to some extent and with metastases in the lungs, liver and kidneys. Sections showed a polymorphous cell sarcoma with many long spindle cell forms; some of the cells contained faint longitudinal striations. The authors called this a rhabdomyosarcoma.

Primary carcinoma of the heart has never been described, but several rather authentic cases of carcinoma originating in the pericardium have been reported.

### VARICES OF THE HEART

Varices, varicose veins, blood nodes or blood cysts are considered because they bear an outward similarity to tumors. In fact, while they are probably due to developmental defects in the new-born or regressive changes in the aged, it is still impossible in certain instances to say positively whether one is dealing with a condition of dilated venous channels or an angioma, as some of these tumors have been called. Husten (1923) collected 31 cases from the literature. The most frequent site for this formation is the rim of the fossa ovalis, especially in the right auricle (23 cases have been reported in the right and 2 in the left auricle). There were 3 instances of varices on the valves, 1 on the pulmonary and 2 on the tricuspid. There were 2 cases of varices on the anterior papillary muscle of the right ventricle and 1 of multiple varices in both ventricles. These varices may be single or occur in small clusters. They may be pedunculated, but are usually sessile and shine through the endocardium as a dark red nodule, rarely larger than a pea. Usually they contain a clot, which may be stratified, and sometimes there is a phlebolith. Some occur in the new-born but most of them are found in adults over 50. According to Nauwerck, in the auricle of adults they may represent hypoplasia of the wall of a vein which lies superficially under the endocardium, or they may be

dilated thebesian veins. Frank suggested that they are due to congenital narrowness of the mouths of these veins. Those on the valves may occur as a failure of regression of the vascular apparatus of fetal life, but Bundschuh, describing one on a pulmonary valve, concluded that the ingoing and outgoing canals open on the surface of the valve. Varices are of no clinical importance.

## PRIMARY TUMORS OF THE PERICARDIUM

All primary tumors of the pericardium are rare. Primary sarcoma of the pericardium has been discussed under the heading of primary sarcoma of the heart, when it was said that 10 of 45 sarcomas were of the pericardium. Also, when discussing lipoma, it was mentioned that several primary sarcomas had been described on the external surface of the heart; these undoubtedly originated from the small fat lobules which are almost always seen in the connective tissue of the pericardium of fat persons (Thorel). The question has been raised (Strüppler) whether these represent an embryonal displacement according to the meaning of Ribbert. Other types of neoplasm have been recorded. Kaufman described lobulated fibrous polyps on the inner surface of a fibrotic, thickened pericardium, the sac of which contained 400 cc. of a serosanguinofibrinous exudate. Jarisch described a papillary tumor of similar appearance which he concluded was the result of organization of a fibrinous exudate. As benign tumors, Orth noted small multiple polypoid tumors of connective tissue containing numerous blood vessels, which may be fibromas or fibrolipomas. Hoch described a tumor which, microscopically, was clearly a phlebogenous angioma.

Of unusual interest is carcinoma of the pericardium. The few cases recorded seem to be instances of endothelial carcinoma derived from the surface cells of the epicardium. Dietrich, Garnieri, Ceelen, and Broadbent (according to Ceelen's interpretation) each reported a tumor of this type. Dietrich's case is rather typical of all: A woman, aged 44, presented at autopsy an enormous bulging of the pericardial sac, which contained 1,500 cc. of dark red fluid. A palm-sized, grayish-red, spongy and crumbly, cauliflower-shaped tumor with many small superficial blood vessels covered the collapsed right auricle. Microscopically, this tumor was of papillary structure with a connective tissue framework containing large vessels, arising from the parietal pericardium; the framework was filled with clusters of large endothelial-like cells with plump, vesicular nuclei rich in chromatin, and the cells were arranged in concentric layers, but without definite perle formation.

A teratoma lying within the pericardial cavity and attached to the root of the pulmonary artery was described by Joel, in 1890.

Keller and Callender described a large neurofibroma attached to the parietal pericardium and apparently originating from the phrenic nerve.

I have seen a cyst, probably of a lymphatic vessel, 4.5 by 2.5 by 2.5 cm., in the pericardial fat at the apex of the heart.

## SYMPTOMATOLOGY

Several authors have discussed this subject, particularly Link, Krehl, Fraenkel, Pavlovsky, Nowicki and Meroz.

For convenience of consideration of the symptomatology, I prefer to make the following division, which is quite different from that of previous authors:

*A.* Clinical types not suggestive of tumor of the heart
  (1) Absence of symptoms referable to the heart
  (2) Symptoms of cardiac embarrassment terminally
  (3) Symptoms of congestive heart failure
  (4) Sudden death
  (5) Symptoms suggestive of subacute bacterial endocarditis

*B.* Clinical types suggestive of tumor of the heart
  (1) Heart block
  (2) Symptoms referable to location of the tumor other than heart block
  (3) Symptoms of cardiac dysfunction developing without apparent cause in a patient with a known malignant process
  (4) Accumulations of hemorrhagic fluid, pericardial and pleural
  (5) Suggestive roentgen observations

In many instances, symptoms of cardiac origin are absent. One can readily see that a small fibroma of a valve or a moderate number of nodules in the myocardium would have little effect on the efficiency of cardiac action, but, as previously mentioned, it is astounding how large the tumors may become, how numerous the nodules or how extensive the infiltration of the myocardium before cardiac function is disturbed. This is particularly true of metastatic growths; in such cases usually death occurs as a result of a widespread malignant process. However, even when the growth is primary in the heart, death may occur as a result of distant secondary lesions without cardiac failure. The case of Beck and Thatcher illustrated well how minor the cardiac symptoms may be and yet how severe the involvement of the heart. The patient was a man, aged 27, in whom the symptoms were all abdominal associated with marked cachexia. There were many subcutaneous nodules, demonstrated to be spindle cell sarcoma and thought to be metastatic. There was a soft systolic murmur over the precordium; the heart rate was 120 and regular, and the blood pressure, 96 systolic and 56 diastolic. These observations were no different than those that might be found in any terminal cachectic state. Death resulted from general peritonitis. The heart and pericardium weighed 1,100 Gm.; 250 cc. of blood was

found in the pericardial sac. There was an extensive sarcoma of the left auricle, several centimeters thick, breaking into the cavity of the auricle and almost filling it as two masses; the sarcoma extended over the left ventricle, and involved the outer portion of the myocardium. A purulent general peritonitis was found, due to perforation of the ileum from a huge sarcomatous mass involving the intestines.

In some cases cardiac insufficiency has been part of the terminal picture, subsequent to a clinical course which did not include symptoms of cardiac breakdown. In such cases the heart has appeared to disintegrate in the final stage of visceral dissolution, and there has not been reason to suspect other disease of the heart.

Symptoms of congestive heart failure develop in a certain percentage of cases, and the clinical course may be entirely that of cardiac decompensation. Usually in such instances the clinician is unable to determine the etiologic factor that is responsible for the heart failure, or he may assign a cause for which he has insufficient evidence. Extensive involvement of the myocardium, obstruction of an orifice or embarrassment of cardiac activity by a pericardial effusion may result in congestive heart failure. Not infrequently with pedunculated intracavitary tumors an orifice, frequently the mitral, may be occluded and the signs of stenotic valvular disease be imitated. In such cases, the diagnosis is given as cardiac decompensation due to chronic endocarditis. The careful clinician may be able to detect certain peculiarities in these cases; these peculiarities will be discussed shortly. An interesting observation has been made that the smaller benign neoplasms are often found in cases in which persons have died of cardiac failure, and in which the tumor could not possibly have played a causative rôle.

Sudden death has occurred in some of the cases reported, either in the course of symptoms of cardiac insufficiency or in the absence of any cardiac symptoms. Usually the sudden death has been apparently due to sudden occlusion of either the mitral or the tricuspid orifice by the penetration of an intracavitary pedunculated tumor. Although strands of cancer cells have been noted loose in the coronary vessels (Moore), and neoplastic thrombosis of the cardiac chambers has been noted (Kanthack, Aubertin, Warthin), it is questionable whether any of the sudden deaths recorded have been caused by metastatic emboli occluding the coronary arteries. Anginal attacks have occurred; in the case reported by Ingram they were followed by sudden death, but it was questionable whether the carcinomatous nodules that had formed in the heart had caused obstruction of the coronary arteries. In the case of Fuhrman (case 1) in which a spindle cell sarcoma of the aortic valve had obliterated the orifice of the right coronary artery and the left coronary artery had been occluded by a plug of tumor tissue, sudden death occurred without previous symptoms except headache.

In a limited number of cases a clinical course practically identical to that of subacute bacterial endocarditis has been recorded. These are usually cases of carcinomatous metastasis involving the cavity of the heart and throwing off showers of small emboli from time to time into the circulation. Examples of this type of course are the cases of Rist and Rolland, of Widal and Abrami and of Carnot and Lambling. The blood culture, of course, is not positive, but this fact is not of great diagnostic importance in bacterial endocarditis and would therefore not be sufficient to rule out this more common condition.

Thus far there has been nothing of diagnostic value in the clinical types discussed. There are, however, clinical features that in certain cases should make one include tumor of the heart in the differential diagnosis. In every case of heart block, especially when complete, one should consider the possibility of tumor when there is no definite cause ascertainable for the arrhythmia. Two cases of lymphangioendothelioma of the auriculoventricular node causing heart block have been described. Armstrong and Mönckeberg's patient was a boy, aged 5½ years, with intermittent complete heart block. In Lloyd's case the patient was a syphilitic Negro, aged 39, with first degree heart block, who died suddenly while being examined. A relatively large number of secondary tumors have been described in which some portion of the conduction system has been involved. The case of Rösler was diagnosed during life as heart block due to metastatic carcinoma; in the ventricular septum under the aortic valve was a walnut-sized metastatic tumor occupying the entire thickness of the septum. A woman, aged 47, had a carcinoma of the cheek with metastases in the right deltoid muscle; while she was in the hospital, precordial pain, a sense of oppression, dyspnea and a feeling of occasional cardiac standstill developed. The heart was not enlarged; the rate was 26 per minute; there was a loud systolic murmur at the apex. Stokes-Adams' attacks occurred in a case carefully described by Luce. In the case reported by Willius and Amberg, the diagnosis of secondary sarcoma of the heart was made during life because of cardiac failure and great hypertrophy of the heart developing in a child known to have a sarcoma of the femur; the electrocardiogram of "left bundle branch block" was obtained. In some instances it has been a matter of wonder why disturbances in conduction were absent in the presence of extensive involvement of the interventricular septum (case of Martin and Klotz). Arrhythmias other than complete heart block are not infrequent but are of no diagnostic value, although in three cases reported by Fishberg the appearance of auricular fibrillation in two and auricular flutter in one associated with orthopnea led to the diagnosis of metastatic invasion of the heart.

When one considers other signs or symptoms referable to the location of the tumor, one finds that certain suggestive evidence is

occasionally manifested. Anomalies of the symptomatology of cardiac disease are not infrequent in tumors of the heart and should lead to careful consideration of etiology. For instance, if a tumor of the left auricle involves the pulmonary veins there may be great embarrassment of the pulmonary circulation, with dyspnea, cyanosis and cough greatly out of proportion to the degree of edema (case of Justi). In one of Binder's cases in which the right auricle was nearly filled by a primary sarcoma, the edema began in the face and extended next to the thorax and lastly to the legs. Likewise in Ehrenberg's case there were dyspnea, cyanosis and edema of the upper half of the body with enlargement of the veins of the sternum; the tumor filled the right auricle and the venae cavae. Often, because of these signs of obstruction of a certain part of the cardiac apparatus, and when the area of cardiac dulness is greatly increased, the diagnosis of tumor of the mediastinum is made. This is especially true in cases of large sarcomas. The symptomatology of large, pedunculated, intracavitary tumors, which are usually of myxomatous and sometimes of sarcomatous nature, is of particular interest. The tumor frequently penetrates and therefore greatly occludes an intracardiac orifice, usually the mitral, less often the tricuspid, and sometimes the pulmonary and aortic. A number of cases of this type, in which the mitral orifice has been obstructed, have been observed. Mitral stenosis or regurgitation have been simulated. Several features, however, may be present to indicate that the case is not the usual one of rheumatic endocarditis. The history of a rheumatic infection is absent; when congestive failure begins, it is progressive; digitalis usually has no effect, and the physical signs may change with change of position. In this last respect the signs may be those of mitral stenosis when the patient is sitting and of mitral insufficiency when he is recumbent, or the murmur may change remarkably within a short time. Göttel quoted Pavlovsky's case of a primary sarcoma of the right auricle, in which during life the diagnosis of a primary tumor of the left auricle had been made, because the signs were those of stenosis when the patient's body was vertical and those of regurgitation when it was horizontal. Sudden attacks of intense dyspnea or paroxysms of cyanosis may occur with change of position. Signs of right auriculoventricular obstruction should arouse suspicion because tricuspid stenosis resulting from inflammation of this orifice is so rare. Likewise, tumor of the heart should be considered when signs of pulmonic stenosis are acquired, since this lesion is almost always congenital. The sessile intracavitary tumors do not often produce these clinical pictures, but occasionally they obstruct an orifice. In sarcomatous intracavitary growths, multiple emboli may be thrown out into either the pulmonary or systemic circulation.

Occasionally, when a person has a recognized malignant neoplasm, the onset of symptoms of cardiac dysfunction, such as arrhythmia or dyspnea or passive congestion, suggests the possibility of metastatic invasion of the heart. Naturally other causes for the cardiac symptoms must be eliminated. In all of the cases thus far diagnosed during life as secondary invasion of the heart, such a situation has existed. The case of Rösler, that of Willius and Amberg, and the three cases reported by Fishberg were diagnosed in this way. The patients of the last named author were all aged between 60 and 70. Two had known primary carcinoma of the bronchi, and auricular fibrillation, orthopnea and finally cyanosis developed. In both, the carcinoma had invaded the posterior wall of the right auricle (in one, also the left) down to the endocardium sufficiently extensively to destroy a large part of the auricular wall and probably the sino-auricular node. In the third case auricular flutter, status anginosus and orthopnea developed in a man with widespread sarcoma of the reticular cells. The walls of the right auricle were extensively invaded down to the endocardium and a nodule 2 cm. in diameter surrounded and obstructed considerably the circumflex branch of the left coronary artery.

The accumulation of bloody fluid in the pericardial sac is highly presumptive evidence of a tumor of the heart. This is a not uncommon finding in sarcoma of the heart in which the epicardium is involved or in which the growth begins in the pericardium. Tumor cells may rarely be found in the fluid. Bloody pleural effusions, while not as definitely suggestive of a cardiac neoplasm, should arouse one's suspicion.

Lastly, a localized enlargement of the heart or an irregularity in its outline associated with enlargement should make tumor of the heart one of the main considerations, together with aneurysm of the heart and mediastinal tumor. These irregularly enlarged hearts have usually been diagnosed mediastinal tumor. The fluoroscope or roentgenogram is naturally of paramount importance in detecting localized enlargements and irregularities.

## SUMMARY AND CONCLUSIONS

Tumors of the heart and pericardium, both primary and secondary, are rare. Metastatic lesions are usually carcinomatous or sarcomatous, and are seen most commonly in cases of widespread dissemination. The primary growth may occur in any organ. Invasion of the heart apparently occurs most commonly by way of the blood stream, and the right side of the heart is more often or more extensively involved than the left.

Primary tumors of the heart are myxoma, fibroma, sarcoma, rhabdomyoma and less commonly lipoma, endothelioma and a few rare forms.

Varices occur in the heart. Nodular leukemic infiltrations are occasionally seen. The myxoma is a pedunculated intracavitary tumor and often reaches sufficient size to obstruct an auriculoventricular orifice. The fibroma is a pedunculated valvular tumor and never becomes very large. The sarcoma may be intramural or intracavitary or both and often becomes extensive. Metastases from sarcoma of the heart are relatively not uncommon. The rhabdomyoma is a congenital tumor of embryonic cardiac muscle and is often associated with tuberous sclerosis of the brain and other developmental disturbances. The patients usually die in infancy or early childhood of conditions not referable to the heart. The lipomas are rarely the cause of cardiac dysfunction. Lymphangioendothelioma of the auriculoventricular node may occur and cause auriculoventricular dissociation.

Primary tumors of the pericardium are usually sarcoma or lipoma. Other tumors have rarely been described, including carcinoma or endothelioma of the surface cells of the epicardium.

The symptomatology may be divided into two classes—that which is not suggestive of tumor of the heart and that which is. In the first class are those cases in which there are no symptoms referable to cardiac dysfunction, those in which there is terminal cardiac breakdown, those in which symptoms of simple congestive heart failure dominate the clinical picture, those in which sudden death occurs with or without previous cardiac symptoms and those in which the clinical picture is that of subacute bacterial endocarditis. In the second class the clinical types may be quite diverse but should serve to call to mind the possibility of tumor of the heart. Any case of heart block in which no satisfactory explanation of the arrhythmia is obtainable may be one of tumor breaking through or originating in the main portion of the conduction apparatus. When symptoms referable to disturbance of function of a portion of the heart occur, tumor of that part of the heart is a diagnostic possibility. In the case of pedunculated intracavitary tumor obstructing a cardiac orifice, usually the mitral or tricuspid, certain deviations from the usual symptomatology of endocarditis are often present. The history of rheumatic infection is absent; the course of congestive failure is progressive; there is little or no response to digitalis, and the physical signs may change remarkably with change of posture. In every case in which tricuspid stenosis seems to be present, tumor should be suspected because inflammatory stenosis of that orifice is exceedingly rare. Acquired pulmonic stenosis should be considered the result of neoplastic obstruction. If in a person who is known to harbor a malignant neoplasm cardiac symptoms develop which cannot be otherwise explained, it is reasonable to assume that metastatic invasion of the heart has occurred. Accumulations of hemorrhagic fluid in the pericardium are

suggestive of subepicardial or pericardial neoplasm, and hemorrhagic pleural effusions are not uncommon in malignant disease of the heart or pericardium. A localized enlargement of the heart or an irregularity of outline associated with enlargement as shown in the roentgenogram are suggestive of tumor of the heart as well as aneurysm and mediastinal tumor.

Few cases of tumor of the heart have been diagnosed during life. Göttel gave Pavlovsky credit for the diagnosis during life of a primary tumor of the left auricle, which in reality was in the right auricle. Rösler and Willius and Amberg made the diagnosis of metastatic invasion, and Fishberg reported three cases of secondary involvement of the heart diagnosed or at least considered a probability while the patients were alive.

Appended are the reports of nine cases of tumor of the heart, five of which are instances of secondary tumor and four of primary tumor.

## REPORT OF CASES

CASE 1.—*Metastatic carcinoma.*

In a Negro, aged 55, a simple deteriorating senile type of psychosis developed in September, 1928. On admission to St. Elizabeth Hospital, it was noted that a tumor the size of two fists, rather soft, mushy and conical, with an ulcerated apex, was located on the left side of the chest posteriorly. This tended to bleed easily, and was considered inoperable. The mass grew rapidly, and the patient gradually declined, dying of bronchopneumonia. The sarcoma on the back had grown to more than 2 Kg. in weight, was sharply outlined, almost encapsulated, and did not seem to be infiltrating the tissues. Microscopically, it showed a rather unusual type of fibroblastoma with extraordinary differentiation. The lungs were not consolidated, but a small metastatic carcinoma was found in the peripheral portion, and some of the hilar lymph nodes were infiltrated. The liver and spleen were not affected. The peritoneum and the kidneys were free. Microscopically, a small carcinomatous nodule was found in the prostate, along with adenomatous hyperplasia. A small primary carcinomatous nodule was found in the pituitary. The anterior surface of the heart showed broad confluent patches of opacity. On the posterior surface of the heart were small nodules extending from the epicardium. The cardiac vessels showed patchy sclerosis. On section the cardiac muscle was firm and fibrous. Microscopic examination showed that the nodules in the heart were of metastatic carcinomatous nature, possibly arising from the primary growth in the prostate. There were clumps of cells rather close together, but separated by one or a few cardiac muscle fibers. These clumps of cells were enclosed in a delicate endothelial sheath, apparently that of a greatly dilated capillary. Mitotic figures were moderately numerous.

CASE 2.—*Metastatic carcinoma.*

A white man, aged 66, was sent to St. Elizabeth's Hospital on account of a suicidal attempt. He was somewhat confused and feeble, and was the subject of paralysis agitans. A roentgenogram of the chest showed a circular opacity in the upper lobe of the right lung which could not be demonstrated by physical examination. After four months with a septic temperature and great

emaciation, the patient died in October, 1930. Necropsy disclosed primary carcinoma of the upper lobe of the right lung with marked degeneration and hemorrhagic infarction. There were secondary nodules in the pleura, the mediastinal lymph nodes and the liver. The heart, besides being rather fibrotic, contained a small shotlike, pearly gray nodule embedded in the anterior wall of the left ventricle. A similar nodule was found in the anterior papillary muscle of the left ventricle and a third superficially in one of the columnae carneae at the base of the right ventricle. Microscopically, the tumor in the lung consisted of polygonal and spindle-shaped cells of unequal size with many gigantic nuclei and numerous mitotic figures. The nodules in the heart consisted of circumscribed masses of similar cells growing between the muscle fibers. In the brain there was secondary implantation in the ependyma in many locations.

CASE 3.—*Metastatic carcinoma.*

A man, aged 53, had been admitted to St. Elizabeth's Hospital at the age of 35, having developed mental symptoms while in the army. In 1906, his left side became paralyzed. In 1914, he began to pick constantly at an abrasion on the left side of the nose. The lesion gradually increased in size. On March 13, 1924, he had a sudden attack of abdominal pain, and died about seven hours later. Necropsy revealed an extensive basal cell carcinoma involving the left orbit and side of the face. There was no involvement of the brain. The peritoneal cavity contained a liter of cloudy greenish fluid, and disclosed active peritonitis due to the perforation of the cardiac end of the stomach by a large carcinomatous lesion. There was extensive carcinomatous metastasis to the peritoneum, but none to the liver. Some of the esophageal lymph nodes were invaded by carcinoma. The lungs were not involved. The heart weighed 470 Gm., was enlarged to the left, and surrounded by 230 cc. of clear pericardial fluid. The organ was greatly distorted, the entire auricular musculature being infiltrated by malignant growth. The walls of the left ventricle were also greatly thickened, and in areas surrounding the coronaries there were dense thickened patches of infiltration. A malignant polyp with a small attachment was found hanging free in the right auricle. There were undoubtedly two distinct lesions, the basal cell carcinoma of the face and the primary adenocarcinoma of the stomach. No slides are available for a review of the case to indicate which of these lesions gave rise to the carcinomatous metastasis in the heart.

CASE 4.—*Hypernephroma of the right auricle.*

An elderly Negro of unknown age entered the Gallinger Municipal Hospital in a greatly emaciated, anemic and weakened condition, and died five days later on April 29, 1928. Necropsy revealed the following conditions: There was a large mass in the right renal region, adherent to the liver, the ascending colon and the duodenum, and apparently originating from the kidney. Dissection showed that the mass was a large hypernephroma (clear celled carcinoma) practically replacing the kidney. The new growth had migrated out through the renal vein, passed up through the vena cava, and terminated in the right auricle, which it practically filled as a yellowish, friable mass (fig. 1). The heart was small and the pericardium contained about 100 cc. of clear fluid. The epicardial fat showed serous atrophy. The coronary arteries were markedly sclerotic. Except for the changes due to coronary sclerosis, the myocardium was normal. The orifices of the heart appeared normal. No other metastases were found. The lungs were edematous.

This case is similar to one observed by me at the Mayo Clinic in 1928, in which the hypernephromatous tissue after filling the right auricle passed upward

through the superior vena cava to the veins of the right side of the neck. There were also large metastatic nodules in the lungs in that case. Clinically, there was no evidence of congestive heart failure, as one might expect.

CASE 5.—*Metastatic melanosarcoma.*

A white man, aged 64, had been confined to St. Elizabeth's Hospital for a mild psychosis since 1922. In 1929, the left eye was removed because of severe pain, and examination revealed sarcoma of the choroid penetrating through the sclera and appearing outside the bulb. Recurrence produced a fungating tumor in the orbit. In spite of removal and cauterization, it grew to be the size of a grapefruit. Roentgen examination showed the entire left orbital bony structure replaced by

Fig. 1 (case 4).—Hypernephromatous tissue completely filling the right auricle through the inferior vena cava.

tumor and metastases in the lungs. Death occurred on Nov. 24, 1930. Necropsy showed extension of the original growth into the left malar bone, left antrum, lateral portion of left nasal fossa, and through the orbital plate into the cranial cavity. A metastatic mass about 4 cm. in diameter was present in the left temporal lobe. In the left lung was a massive black metastatic lesion, 9 by 8 by 6 cm., and a small one near the hilus of the right lung. A large mass was found medial to the left kidney. Nodules as large as 6 cm. in diameter were present in the omentum adherent to the peritoneal coat of the intestine, particularly in the region of the cecum, and there was one small nodule in the submucosa of the colon. Two nodules were embedded in the tail of the pancreas. The heart was of normal size, the epicardium was rather fatty, and the myocardium was soft, fine in texture and translucent. In the posterior part of the interauricular septum on the right side, fairly close to the auricular appendage, were two small shotlike

nodules resembling embedded lead shot, occupying the muscular tissue and showing through into the cavity. Microscopic examination showed that the primary and larger secondary lesions consisted of groups of cells containing a variable amount of pigment, tending to necrosis in the center and to widespread extension externally. The nodules were rather richly supplied by thin-walled blood vessels. The small nodules in the heart consisted of a mass of similar cells infiltrating the auricular musculature (fig. 2). The nuclei of the cells were large and hyperchromatic. The tumor was a melanosarcoma. A microscopic metastatic nodule

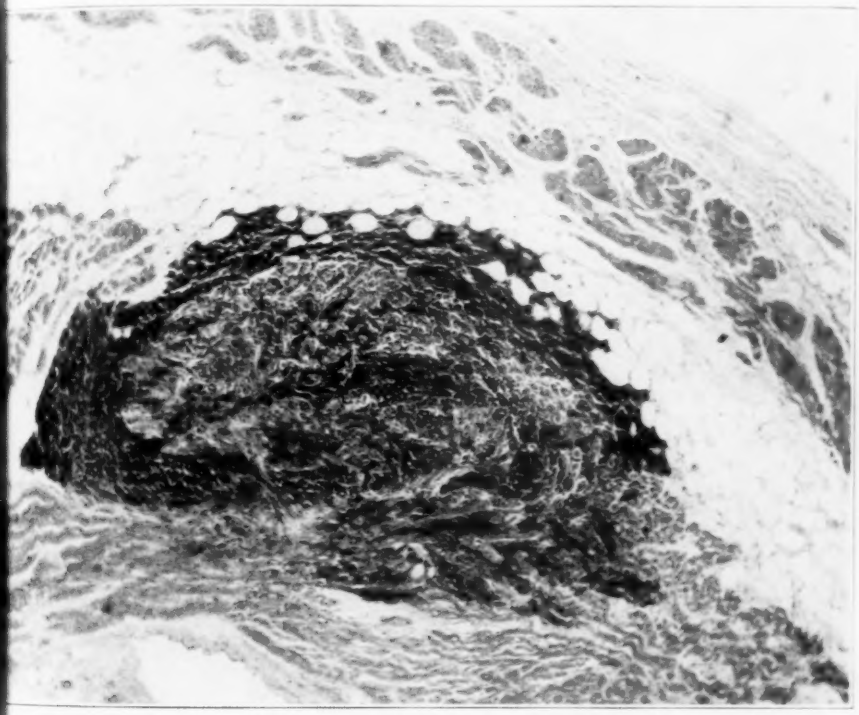

Fig. 2 (case 5).—Photomicrograph of metastatic melanosarcoma in the wall of the right auricle; reduced from a magnification × 85.

was found in the suprarenal. In addition to the primary growth of the eye with its multiple metastases, there were a papillary cystadenoma of the renal cortex of doubtful malignancy and a small primary growth probably of adenocarcinomatous type in the hypophysis.

CASE 6.—*Myxoma of the left auricle.*[2]

A woman, aged 23, came to the clinic on June 16, 1927, complaining of shortness of breath, palpitation and weakness for a period of two years. The onset

2. This case has been previously reported (Barnes and Yater: M. Clin. North America **12**:1603, 1929).

of symptoms had not been acute or definite; they had become distinctly worse in the last six months with some swelling of the ankles and feet at the end of the day. Nausea, vomiting and gaseous distention in the epigastrium constituted the chief complaint on admission. The previous history was not significant, and rheumatic infection was not known to have occurred.

Examination of the heart showed a presystolic murmur and thrill at the apex and a systolic apical murmur transmitted to the axilla. The second pulmonic sound was markedly accentuated. There was moderate cyanosis of the lips and nails. The laboratory data were not significant, except that a teleoroentgenogram showed evidence of definite cardiac enlargement. The electrocardiogram showed a rate of 80, a notched Q R S wave in derivation III and left ventricular preponderance.

Fig. 3 (case 6).—Pedunculated myxoma of left auricle, bisected, showing hemorrhages in the substance of the tumor.

The patient's response to the administration of digitalis and to every effort at treatment was not satisfactory, and her course was progressively downward. She died from cardiac failure twenty-nine days after admission.

The usual conditions of chronic passive congestion of the liver and spleen, ascites and hydrothorax, and pulmonary infarcts were found. The heart weighed 374 Gm. In the left auricle, attached by a broad base to the interauricular septum in the region of the fossa ovalis, was an elongated, irregularly round, gelatinous looking tumor which measured 6 by 4.5 by 3.5 cm. It practically filled the auricle and its lower fourth almost occluded the mitral orifice. On the surface of the tumor were a few small areas of hemorrhage; when the mass was bisected, the cut surface resembled colloid material and was hemorrhagic (fig. 3). The

ventricles were both markedly dilated, particularly the right, and the walls of the latter chamber were considerably hypertrophied. The valves appeared normal, except for small terminal vegetations on the tricuspid. The coronary arteries were smooth. This was microscopically a myxoma. Stained with hematoxylin-eosin, the matrix was a pale, pinkish, granular or fibrinous substance. In it were numerous cords of endothelial-like cells, often appearing like a syncytium. The

Fig. 4 (case 6).—Photomicrograph of myxoma, showing small hemorrhages and cords of endothelial-like cells in a mucoid matrix; × 225.

nuclei were light, oval, vacuolated and rather large. These groups of cells were in general placed with their long axis in the same direction. They tapered at the ends, the nuclei were numerous and close together, and the cytoplasm was rather pale. Delicate blood vessels were present in the tumor, but were not especially numerous. One contained a fibrinoid thrombus. Groups of erythrocytes were scattered through the sections, and were more numerous toward the center of the

tumor (fig. 4). Hemosiderin was present in the cytoplasm of some of the cellular syncytia and in what appeared to be plasma cells scattered through the sections. Lymphocytes were seen here and there, and less numerous polymorphonuclear leukocytes occurred, clumped in small groups widely separated.

Both grossly and microscopically, this case closely resembled another case studied by me in 1928 at the Mayo Clinic. In that case, however, the patient, a woman, aged 34, died of septicemia following a self-induced abortion. She had increasing but not especially severe dyspnea on exertion for two years and a systolic apical murmur.

CASE 7.—*Hyaline fibroma of the aortic valve.*

A Negro, aged 70, entered the Georgetown University Hospital in a greatly emaciated condition. Two months previously, speech had become impaired and

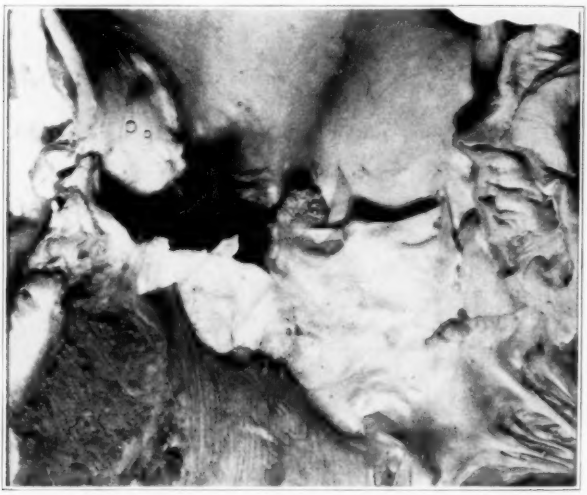

Fig. 5 (case 7).—Papilloma (hyaline fibroma) of the aortic valve.

ability to walk was lost. Examination revealed a rapid, feeble pulse, generalized moist râles in both lungs, inability to articulate or swallow and right hemiplegia. Death occurred three days after admission, May 6, 1929. Necropsy revealed nothing of unusual interest except in the heart. On the edge of the noncoronary cusp of a somewhat sclerotic aortic valve, projecting up into the aorta when the valve was closed, was a rounded, extremely villose, grayish-pink tumor, about 0.8 cm. in diameter, attached to the valve by a short pedicle (fig. 5). Microscopically, this papilloma was seen to spring from the subintimal connective tissue by several small roots. The valve in this region was microscopically otherwise normal. The tumor was completely invested by a single layer of endothelial cells continuous with the intima of the valve. It was completely avascular (fig. 6). The ground substance was homogeneous, pale and slightly eosinophilic (hematoxylin-eosin stain). Some of the villi contained denser centers of circular or oval shape, which showed dense accumulations of broken elastic fibers arranged in layers (Weigert's elastic stain). In the ground substance of some of the villi

were a few, somewhat round cells with an ovoid, rather dark, often eccentric nucleus and a fair amount of cytoplasm. The matrix of the tumor stained light purple with van Gieson's stain. Other special stains did not show anything of unusual interest. This tumor might be designated a hyaline fibroma.

CASE 8.—*Fibromyxoma of the aortic valve.*

A white man, aged 65, entered the Georgetown University Hospital on Nov. 15, 1930, and died on November 23, of empyema of the left pleural cavity. Clinically, the case was interesting because the empyema was due to the colon bacillus;

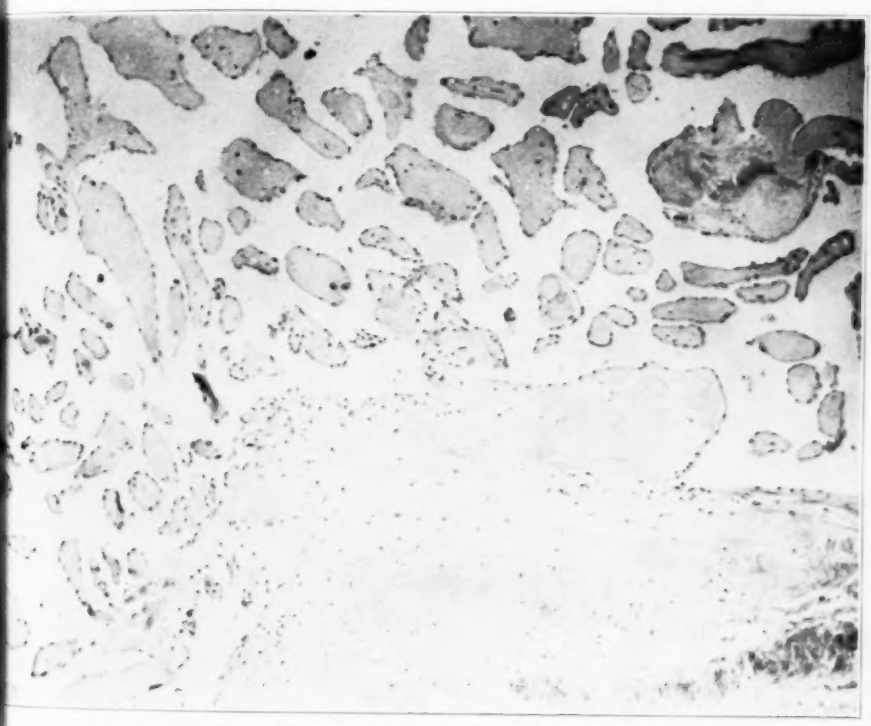

Fig. 6 (case 7).—Photomicrograph of papilloma of the aortic valve through the pedicle; reduced from a magnification × 112.

otherwise there was nothing especially remarkable except that the patient gave a history suggestive of duodenal ulcer. Necropsy revealed the empyema and a large duodenal ulcer. The heart was normal except for a papilloma attached by a short, delicate pedicle on the aortic side of the right coronary cusp of the aortic valve near the free edge and 0.5 cm. from the posterior commissure of the cusp. It was pink, villose, soft, rounded, freely movable and a little under 0.5 cm. in diameter. Delicate Lambl's excrescences were present also on the nodules of Arantius of all three cusps of the aortic valve. There was no evidence of inflammatory change. Microscopically, the tumor was seen to resemble closely that in

case 10, which it resembled grossly also. It was a papillary fibromyxoma and was completely avascular. The numerous small villi were covered by a single layer of endothelial cells. The matrix streamed forth from the subendothelial connective tissue of the valve through a short pedicle. In most of the villi the matrix was a delicate myxomatous tissue with scattered star cells. In the center of many of the villi the ground substance was more dense, homogeneous, fibrillar or granular and eosinophilic. When stained for elastic tissue, delicate fibrils of elastin and small granules appearing to be products of disintegrated elastic fibrils were seen in these cores.

CASE 9.—*Congenital rhabdomyoma.*

A colored girl, aged 5, had had convulsive attacks two years before death, but the attacks had not recurred until two days before her final admission to Ancon Hospital. On admission, she was unconscious, and showed twitching of the muscles, especially of the left side of the body. Flaccid paralysis of the left arm with spastic paralysis of the right arm and difficulty in swallowing developed a few days after admission. The muscular twitchings continued, but the child could be partially roused from her stupor. The spinal fluid was clear with five cells; the Wassermann reaction was negative and pressure was diminished. The patient died twenty-two days after admission, on Sept. 13, 1927. Necropsy revealed nothing of note except in the brain, kidneys and heart. The convolutional pattern of the cerebrum was normal but there was considerable variation in the depth and width of the individual gyri, many of which showed focal flattening and widening. The distorted areas were extremely firm on palpation, and on section the firm areas presented a smooth white surface which showed no trace of the cortical gray matter. These areas were irregular in shape and were on the average from 1 to 2 cm. in longest diameter. They were scattered throughout the cerebral hemispheres and basal nuclei and there were small nodules of similar tissue in the brain stem, medulla and cord, but not in the cerebellum. The tissue of the brain, except in these areas, was slightly congested, but appeared otherwise normal. Microscopic examination of the firm areas showed diffuse gliosis with reduction or absence of nerve cells. The glial tissue was rich in fibrils and the glial nuclei were not excessive in number (tuberous sclerosis). The kidneys appeared normal except for diffuse involvement with yellowish-white, vascular nodules resembling grossly small conglomerate tubercles. Microscopic section showed that these nodules were interesting examples of mixed tumor of the Wilm's type. There were also small cystadenomas in the kidneys. The heart weighed 85 Gm. The muscle was pale brownish red and fairly firm. There was a yellowish-white nodule in the interventricular septum which measured 1 cm. in diameter and projected approximately 0.5 cm. subendocardially into the left ventricle. There was a smaller, flat, subendocardial nodule in the wall of the right ventricle. On section, the cut surface of the nodules was yellowish white, homogeneous and translucent. They were sharply outlined, but not encapsulated. The valves and chambers of the heart did not show anything else worthy of note. Microscopically, a typical rhabdomyoma was seen in the heart. The subendocardial nodules were well circumscribed, and except in a few small areas were separated from the myocardium by a layer of connective tissue. The nodule in the interventricular septum was separated into two main portions by a trabecular connective tissue; one portion projected into the ventricular cavity subendothelially. Under low magnification, the tumor looked like a strongly reticulated tissue from which most of the sarcoplasm had been dissolved, leaving only the framework of the connective tissue and the nuclei. Van Gieson's connective tissue stain, however,

revealed that there were practically no fibers of connective tissue present. The supposed reticulum constituted the thin sarcoplasmic shells of large, relatively empty cells in which were large, fairly round nuclei lying in a central island of sarcoplasm attached to the shell by a fine supporting network of sarcoplasm. The nucleus was densely granular, and contained a large nucleolus. Some of the cells contained two nuclei in close proximity. The outlines of the cells indicated that the cells varied somewhat in size and shape, but were irregularly round and more or less of the same size. Between these large cells, small, ovoid, dark nuclei were

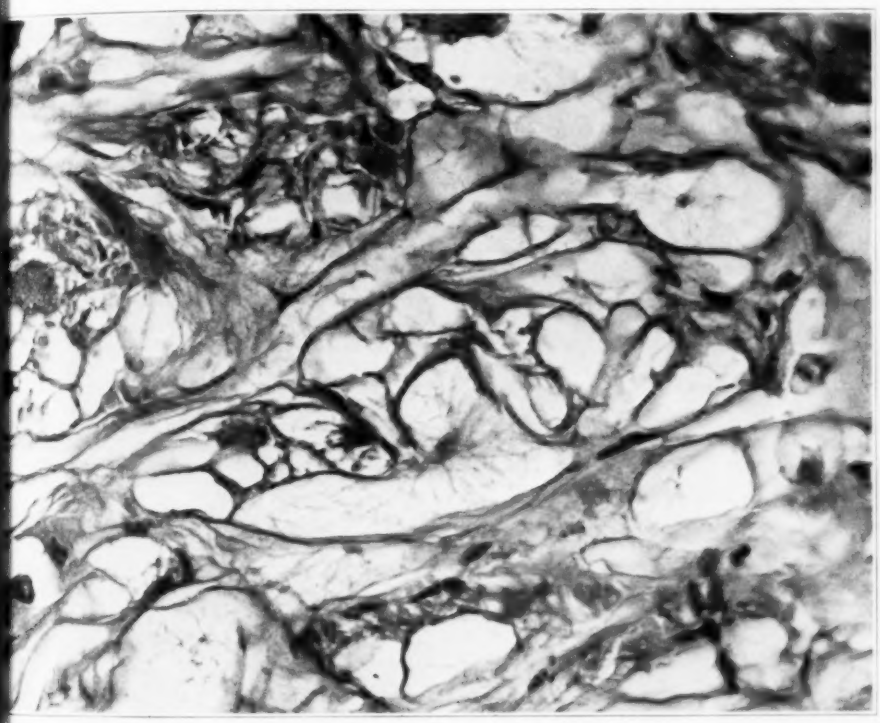

Fig. 7 (case 9).—Photomicrograph of a congenital rhabdomyoma of the heart. In the upper left-hand corner is seen an adult cardiac muscle fiber in the midst of rhabdomyoma cells; reduced from a magnification × 765.

intermittently embedded in a little sarcoplasm. Also, occasionally between the large, protoplasmically poor cells, bodies were seen that resembled the nuclei of normal adult myocardial fibers. Where such nuclei were present there might be a denser accumulation of sarcoplasm with parallelly running fibrils, so that a cardiac muscle fiber was suggested (fig. 7). Cross-striations were faintly visible in some of these areas. These denser accumulations of sarcoplasm appeared to have more or less the same general direction of their longitudinal axes. At one side of the nodule in the septum, part of the left bundle branch lay exceedingly close to the

edge of the tumor nodule and was barely separated from it by the finest connective tissue fibers. This gave an excellent opportunity to study the two types of tissue, the Purkinje fibers and the rhabdomyoma cells. While there was a superficial resemblance, more careful study showed the two tissues to be quite different. Running through the tumor nodule a few scattered delicate fibrous trabeculae were seen supporting the tissue and the small blood vessels. At the edge of the nodule where the myocardium was in direct contact, a definite transition between the two tissues was not apparent.

NOTE.—Since this article was written I have observed two further cases of tumor of the heart.

The first patient was a psychotic woman, aged 69, who was found at necropsy to have a carcinoma of the gallbladder with metastases to the lungs, liver, ovaries, suprarenal glands and heart (St. Elizabeth's Hospital, autopsy no. 5631). On microscopic section, two small nodules made up of rather large polygonal cells were found in the heart; they resembled those of the other metastases. One nodule was located in the subepicardial fat, while the other was in the myocardium. Both were infiltrating.

The second patient was a man, aged 51, who was thought to have a primary pulmonary neoplasm with metastases to the liver. At necropsy (Georgetown University Hospital, autopsy no. 34-Y-31), a large bronchiogenic carcinoma of the left lung was found which had extended into and replaced the wall of the left auricle down to the endocardium. The tumor of the lung had so surrounded and compressed the pulmonary artery that its lumen appeared like a slit. During life, significant cardiac dysfunction had not been noted. A detailed report of this case will be given elsewhere.

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# FUNCTIONAL ASPECTS OF REGENERATED HEPATIC TISSUE*

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It is common knowledge that the liver surpasses most, if not all, glandular organs in its power to replace substance lost through disease. The anatomic processes involved in reconstruction of hepatic parenchyma after spontaneous or experimental injury to the liver have been well described by many investigators.[1] However, little is known concerning the functional capacity of regenerated hepatic tissue.

A new approach to this important subject was opened by recent progress in tests of renal function, two of which were instrumental in the present contribution to the knowledge of pathologic physiology. The first of these, the rose bengal dye excretion test,[2] is based on the selective elimination, via bile channels, of this dye when given intravenously. Retention of rose bengal in the blood above 60 per cent at the end of eight minutes and over 30 per cent after sixteen minutes is indicative of decreased permeability of the hepatic cells or of obstruction to the free flow of bile. The second, a modification of the dextrose tolerance test,[3] in which insulin and a large amount of water are given to the patient in addition to dextrose, depends on the carbohydrate metabolism-regulating function of the liver. A blood sugar level below 70 mg. per hundred cubic centimeters at the conclusion of this test indicates incompetence of the carbohydrate-regulating mechanism of this organ.

These tests, in my experience, covering over sixty cases, have given very similar estimates of the functional state of the liver in health and in various diseases of the liver. However, in five patients with obvious

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1. For a good bibliography see Schultz, E. W.; Hall, E. M., and Baker, H. V.: Repair of the Liver Following the Injection of Chloroform into the Portal System, J. M. Research **44**:207, 1923-1924.

2. Epstein, N. N.; Delprat, J. D., and Kerr, W. J.: The Rose Bengal Test for Liver Function, J. A. M. A. **88**:1619 (May 21) 1927.

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hepatic disease and marked retention of rose bengal dye, the carbohydrate metabolism-regulating mechanism of the liver was found to be within normal limits, as indicated by the modified dextrose tolerance test. In three of these cases, the histories of which are briefly summarized, the liver was examined pathologically, making it possible to bring them together under one pathologic entity. This entity, namely, toxic cirrhosis of the liver, can now also be recognized clinically by the contrast between evidence of hepatic damage with marked retention of dye and preservation of normal carbohydrate metabolism regulation.

## REPORT OF CASES

Case 1.—A Swedish stevedore, formerly a sailor, aged 53, was admitted to the University of California Hospital on Dec. 18, 1928, with a complaint of swelling of the legs and abdomen which came on after exposure during a rainstorm five days before entry. This swelling was accompanied by cramplike abdominal pains, dyspnea and palpitation. At the same time he noticed a diminished output of urine, nocturia and distention after meals. He admitted that he used alcohol moderately.

On examination, there was vitiligo on his arms. The cervical lymph nodes were palpable. The right pupil was small and fixed; the left pupil reacted slowly to light and accommodation. There were signs of fluid at the bases of both lungs. The abdomen was distended with fluid; no organs could be felt, even after paracentesis. The patellar and achilles reflexes were absent. Slight pressure on the prostate produced mucopurulent fluid at the urinary meatus. The urine and purulent prostatic fluid were loaded with pus and contained numerous intracellular and extracellular gonococci. An examination of the blood showed a moderate leukopenia with a normal differential count. The Wassermann test of the blood was negative, but the Kahn test was reported 2 plus. The nonprotein nitrogen of the blood was 44.8 mg. per hundred cubic centimeters. Fluid having the characteristics of transudate, with a specific gravity of 1.010 and a negative Wassermann reaction, was removed from the abdomen and chest in amounts of 4,000 and 1,400 cc., respectively. A lumbar puncture gave negative results, including the Wassermann reaction. The rose bengal test for hepatic function showed a retention of 95 per cent of the dye at the end of eight minutes, and 83 per cent at the end of sixteen minutes. A modified dextrose tolerance test gave a normal curve with a blood sugar of 83 mg. per hundred cubic centimeters at the end of three hours.

Two weeks after the first paracentesis, the abdomen was again distended with fluid. At this time the patient vomited about 250 cc. of dark red blood, and a few minutes later also passed blood by rectum. Three days later, he failed to urinate for twenty-four hours. Since multiple strictures of the urethra made catheterization impossible, suprapubic cystotomy was performed, but only 60 cc. of urine was found in the bladder. Five hours after the operation, the patient died with evidence of another esophageal hemorrhage. During his stay in the hospital he was afebrile.

The main clinical diagnosis was portal cirrhosis of the liver. At autopsy, performed by Dr. J. F. Rinehart, the liver was found to weigh 1,090 Gm. Its surface was strikingly nodular and granular, having a greenish-yellow appearance. Microscopically (fig. 1), it showed a marked fibrosis of irregular distribution and adenomatous areas of hepatic cells. The hyaline droplets described in alcoholic cirrhosis by Mallory were not seen. The kidneys were essentially normal.

The main pathologic diagnosis was toxic cirrhosis of the liver.

CASE 2.—An Irish crane operator, aged 45, entered the University of California Hospital on June 8, 1929. He had been well up to three weeks before admission when general malaise and anorexia developed. A few days later the patient noticed a gradually increasing yellow discoloration of his skin, accompanied at times by sensations of fever. At the same time his stools became light, and the urine assumed a very dark color. Five days prior to entry, swelling of the ankles and abdomen appeared.

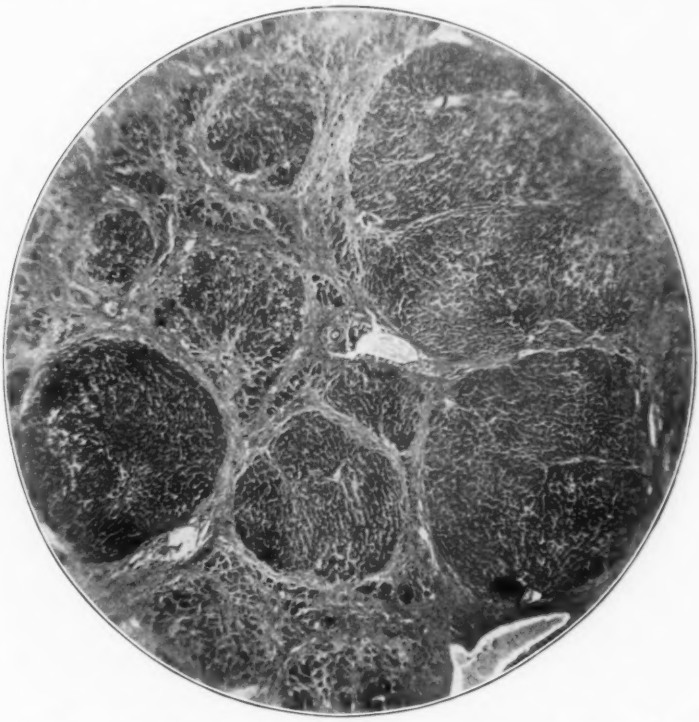

Fig. 1 (case 1).—Section of the liver showing marked fibrosis of irregular distribution and adenomatoid areas of hepatic cells; × 22.

On physical examination, the patient presented a picture of deep icterus. He had bilateral ptosis of the upper eyelids, more marked on the right. The diaphragm was high, and there were signs of congestion at the base of the right lung. The abdomen was moderately distended, and no organs were felt. There was moderate edema of the lower extremities. The blood showed a leukocytosis of 11,400 with 76 per cent of polymorphonuclear neutrophils. The Wassermann and Kahn tests of the blood were negative. The icterus index was 190. In the urine were found much bilirubin and some urobilin. The stools were light brown. Three days after entry, the patient developed signs of fluid in the abdomen, which was tapped, and

2,200 cc. of fluid was obtained. The ascitic fluid was a typical transudate with a specific gravity of 1.008 and a negative Wassermann reaction. A modified dextrose tolerance test showed a normal blood sugar curve with the reading of 122 mg. per hundred cubic centimeters at the end of three hours. The rose bengal test for hepatic function was not done in view of deep jaundice. In the hospital the patient grew rapidly worse and, passing through a delirious stage, died on the sixth day in coma. There was a terminal rise of rectal temperature to 38.5 C. (101.3 F.).

Fig. 3 (case 2).—Section of the liver taken from the red marginal zone and showing complete parenchymatous destruction with remaining bile ducts; × 48.

The main clinical diagnosis was cirrhosis of the liver (nature undetermined), with cholemia.

At postmortem examination, performed by Dr. J. F. Rinehart, the liver was found to be very small, weighing only 840 Gm. Scattered over the surface were small, grayish, elevated nodules (fig. 2). On section, the right lobe of the liver showed a narrow marginal zone of red tissue containing minute gray areas. The central portion of the liver was composed of greenish regenerated tissue having a nodular arrangement. Most of the left lobe consisted of dense red tissue; but it, too, contained nodules of regenerated parenchyma.

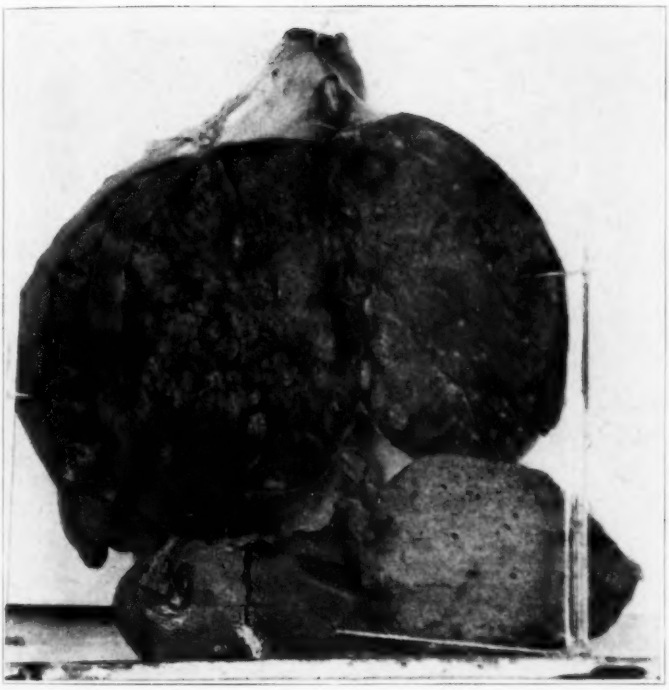

Fig. 2 (case 2).—The red marginal zone of the liver shows complete parenchymatous destruction. The central bile-stained portion of the liver represents regenerated hepatic tissue without lobular arrangement.

Under the microscope, the red marginal zone (fig. 3) showed complete parenchymatous destruction, but the framework with its portal spaces and central veins remained. Tissue from the central portion of the liver (fig. 4) showed hyperplastic nodules of regenerated parenchyma in which lobular arrangement was entirely lost. These nodes of varying size were separated by bands of fibrous tissue. Biliary stasis was distinctly shown in the canaliculi near the margin of the nodules.

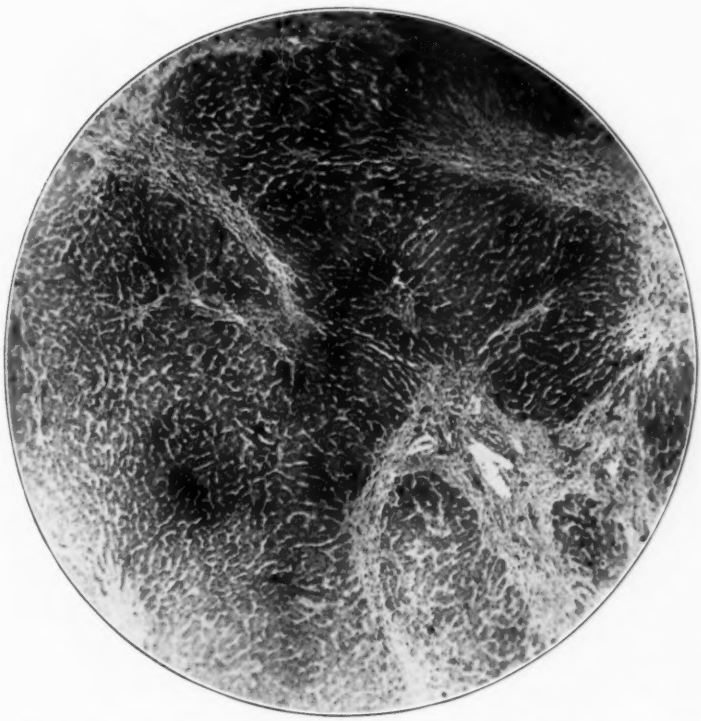

Fig. 4 (case 2).—Section of the liver taken from the central portion of the liver and showing regenerated parenchyma without lobular arrangement; × 48.

The principal pathologic diagnosis was subacute atrophy of the liver with regenerative hyperplasia and early toxic cirrhosis.

Case 3.—A chorus girl of Norwegian extraction, aged 17, was admitted to the University of California Hospital on Jan. 15, 1929, with complaints of jaundice and amenorrhea. Late menstruation and sterility were characteristics of the female members of her father's family. During the past three years, the patient had four or five attacks of jaundice with chills, fever, marked abdominal distention and nausea. The two last attacks were also associated with sharp pains in the right upper quadrant. At the time of entry, she had had generalized abdominal pain

and tenderness for one month and distention for two months. During the past year, the patient had epistaxis two or three times weekly. In her occupation she used as a whitening substance, a toilet preparation, "Shady Glen," all over her body several times a day, instead of once as did the other chorus girls, because this compound underwent greenish-blue discoloration on her skin. On physical examination, she showed moderate icterus and some girdle obesity. The edge of the liver was tender, and the spleen extended 3 cm. below the costal margin. The breasts and genitalia were infantile. The blood showed moderate secondary anemia, with a reticulated cell count of 1.5 per cent. The Wassermann and Kahn tests of the blood were negative. Repeated fragility tests showed normal resistance of erythrocytes. The icterus index varied between 15 and 25. A qualitative van den Bergh test gave a delayed direct reaction. The urine contained some urobilin, but no bilirubin. During her stay in the hospital she was afebrile and there was some improvement.

The main clinical impression at this time was acquired (Hayem-Widal) type of hemolytic icterus.

Two months later the patient reentered the hospital because of an attack similar to the first. The physical examination gave the same results, except for signs of fluid in the abdomen which proved to be a transudate with a specific gravity of 1.010. A rose bengal test for hepatic function showed 100 per cent retention of the dye. A modified dextrose tolerance test indicated moderate impairment of carbohydrate metabolism with a blood sugar level of 52 mg. per hundred cubic centimeters at the end of three hours.

This new evidence of severe hepatic damage was interpreted as favoring a diagnosis of Banti's disease with secondary cirrhosis. For this reason splenectomy was performed. At operation, the liver was found to be very small and contained large nodules of regenerated tissue, some of which were almost pedunculated. Microscopic examination of an excised wedge of hepatic tissue (fig. 5) showed fibrous tissue infiltrated with lymphocytes and adenomatous nodules of hepatic cells lacking normal architecture.

The pathologic diagnosis was cirrhosis of the liver, toxic in origin, with secondary splenomegaly.

Since her discharge from the hospital, the patient has been in fairly good condition provided she is relieved every two to three weeks of about 7 liters of ascitic fluid. Seven months after the patient's second hospitalization, both tests for hepatic function were repeated. On this occasion, the rose bengal test showed a retention of 92 per cent of the dye at the end of eight minutes, and 84 per cent at the end of sixteen minutes. The modified dextrose tolerance test gave a normal blood sugar curve with a terminal blood sugar level of 79 mg. per hundred cubic centimeters of blood.

## COMMENT

The clinical diagnosis in the first reported case was portal (Laennec's) cirrhosis of the liver. Marked retention of rose bengal dye was entirely in keeping with this diagnosis, but the normal response to the modified dextrose tolerance test was contrary to my previous experience with patients having portal cirrhosis. When the patient died the original pathologic diagnosis also was portal cirrhosis. All steps of the modified dextrose tolerance test were retraced, but no mistakes in technic were discovered, and the discrepancy could not be accounted for.

Several months later, the patient in case 2 was seen, and a clinical diagnosis of cholemia due to cirrhosis of undetermined nature was made. The rose bengal test in this case was superfluous because of the presence of deep jaundice, which is always accompanied by retention of the dye roughly in proportion to the degree of jaundice. A modified dextrose tolerance test was performed, and, contrary to expectation, indicated normal carbohydrate metabolism. Postmortem examination revealed subacute atrophy of the liver with regenerative hyperplasia and early toxic cirrhosis.

The appearance of the liver which, as shown in figure 2, consisted mostly of newly regenerated, bile-stained tissue, suggested that the contrast between clinical cholemia and a normal carbohydrate metabolism may be explained on the basis of the new liver cells having no connection with the biliary tree. If this were correct, the liver would be severely handicapped in the performance of its excretory functions. At the same time, the new tissue having an efficient circulation of blood would be capable of performing its metabolic functions and among them those of glycogenesis and glycogenolysis.

Microscopic examination of tissue from various parts of the liver confirmed this hypothesis by showing complete destruction of parenchyma in the red marginal zone (fig. 3) and biliary stasis and absence of lobular arrangement in the hyperplastic nodes of regenerated cells (fig. 4). The bile-stained appearance of the new hepatic tissue in toxic cirrhosis and the apparent lack of biliary capillaries in the hyperplastic nodules were mentioned by Mallory,[4] who was the first to describe this type of cirrhosis, ascribing it to repeated attacks of subacute yellow atrophy of the liver. More recently, the same features were emphasized by Pratt and Stengel,[5] and by Connor.[6]

Since the foregoing observations brought into harmony all clinical and laboratory data in the second case, at first so puzzling, the necropsy material of the first case was reviewed (fig. 1) with the result that the pathologic diagnosis was changed from portal to toxic cirrhosis of the liver.

The third patient, who fortunately is still alive, furnished one more aspect of the unfolding panorama of functional hepatic regeneration in toxic cirrhosis. The first clinical diagnosis in this case was acquired hemolytic icterus (Hayem-Widal type), which was later changed to

4. Mallory, F. B.: Cirrhosis of the Liver: Five Different Types of Lesions from which It May Arise, Bull. Johns Hopkins Hosp. **22**:69 (March) 1911.

5. Pratt, J. H., and Stengel, A.: Toxic Cirrhosis Resulting from Acute Liver Atrophy, Tr. A. Am. Physicians **41**:100 (May) 1926.

6. Connor, C. L.: Toxic Cirrhosis of the Liver, Canad. M. A. J. **17**:546 (May) 1927.

Banti's disease. The rose bengal test showed complete retention of the dye in the blood stream, indicating total loss of permeability on the part of the liver. On the other hand, the modified dextrose tolerance test indicated only moderate disturbance of carbohydrate metabolism. During operation for removal of the spleen, advanced cirrhosis of the liver was discovered which, with the help of a biopsy specimen from the liver (fig. 5), was identified as belonging to the toxic group.

Fig. 5 (case 3).—Section of biopsy specimen from the liver showing great loss of hepatic substance around an adenomatoid nodule of hyperplastic cells; ×48.

Seven months later both hepatic function tests were repeated. The rose bengal test still showed marked, though not complete, failure in the excretion of dye, but the modified dextrose tolerance test this time gave a normal blood sugar curve. This patient demonstrated that during the acute stage of toxic cirrhosis of the liver, both the excretion of dye and the regulation of the carbohydrate metabolism are impaired, the former much more than the latter, probably because regeneration in the

liver is taking place simultaneously with necrosis, though not keeping pace with it. On the contrary, in the chronic stage regeneration of new hepatic cells predominates and the metabolic functions of this organ proceed in a normal manner.

It is significant from the point of view of establishment of proper drainage of bile of the new hepatic tissue that seven months after the acute attack, when sugar metabolism had returned to normal, grave impairment of the excretion of dye, comparable in its severity to that in the two fatal cases, still existed.

Whether excretory channels ever become available to regenerated parenchyma in toxic cirrhosis of the liver is an interesting question that I hope to be able to answer by following the third patient longer. The slight return of the ability to excrete dye observed in this case so far does not prove anything, because it can be accounted for by subsiding inflammation and edema, which accompany necrotic processes and which would contribute to retention of dye during the acute stage.

The present work makes possible clinical differentiation between toxic cirrhosis of the liver and a number of other conditions, principally portal cirrhosis, by demonstrating in the former normal carbohydrate metabolism and at the same time marked retention of dye.

The difficulties of diagnosis in this disease are evident. A history of intermittent jaundice appears to be the only differential symptom of value in toxic cirrhosis, and this feature is not a constant manifestation, appearing only once in the three cases here reported. In none of these cases was the diagnosis made clinically, although opinions were given by several competent consultants. The same is true of the cases reported by Connor.[7] Any test, therefore, which will assist in the diagnosis of toxic cirrhosis will probably find a wide field of usefulness in the study of diseases of the liver.

## SUMMARY

1. In toxic cirrhosis of the liver, vigorous regeneration of tissue maintains the carbohydrate metabolism-regulating function and probably other metabolic activities of this organ.

2. Owing to a loss of the original structure of the liver in this disease, the new hyperplastic nodules lack connection with bile channels, accounting in this manner for marked impairment in the excretion of dye.

3. This information can be utilized by the clinician for differential diagnosis of toxic cirrhosis of the liver by the use of two suitable tests of hepatic function.

7. Connor, C. L.: Personal communication.

# NORMAL ASYMMETRY AND UNILATERAL HYPERTROPHY *

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The question of bilateral asymmetry of the human body has been the subject of numerous investigations and researches on the part of anatomists, anthropologists and archeologists of the past century. As a result of exact measurements taken from a great number of cadavers and living subjects, it has been established that the two halves of the body in the human species, as well as in the higher vertebrates, are in reality never symmetrical. This fact being established, a more detailed study of various asymmetries followed.

Meckel [1] was the first anatomist to treat the subject in a scientific manner. Various asymmetries and their physiologic significance were exhaustively treated by von Bardeleben [2] in a paper presented by him before the Anatomische Gesellschaft in 1909. A French investigator, Richard Liebreich,[3] made a most painstaking study of skulls and faces of various races and various periods. In contradistinction to the well-known views of Lombroso and Nordau, Liebreich reached the conclusion that asymmetry of the skull and face is a constant and characteristic feature of the human species. He found that Negroes presented less asymmetry than white persons, and that generally speaking the higher the scale of civilization the more pronounced was the facial asymmetry.

It is now common knowledge that the left cerebral hemisphere, the left half of the skull and the left side of the face are larger than those of the right. The left frontal bone is better developed and projects further forward. The left cheek and the left half of the lower jaw are more prominent. On the other hand, the right halves of the vertebral bodies, as well as the ribs of the right side, are larger than those of the left. In at least 70 per cent of cases, the right half of the sternum is larger than the left. Measurements of the bones of

* Submitted for publication, Jan. 7, 1931.

1. Meckel, J. F.: Ueber die seitliche Asymmetrie im tiereschen Körper, Anatomische physiologische Beobachtungen und Untersuchungen, Halle, Renger, 1822, p. 147.

2. von Bardeleben, Karl: Ueber bilaterale Asymmetrie beim Menschen und bei höheren Tieren, Verhandl. d. anat. Gesellsch., Jan. 23, 1909; Anat. Anz. **34**:2, 1909.

3. Liebreich, Richard: Die Asymmetrie des Gesichtes und ihre Entstehung, Munich, J. F. Bergmann, 1908.

the upper extremities demonstrate that the bones of the right side are somewhat longer and slightly thicker than those of the left. The length of the right upper extremity may exceed that of the left by 1 cm., or even by 2 cm.

The situation is reversed for the lower extremities, the left leg more often being longer and stronger than the right, an instance of crossed asymmetry. Cox [4] found that in living subjects the difference in the length of the lower extremities amounted to from one eighth to seven eights of an inch, and that the left extremity was more often the longest. That the pelvis is practically never symmetrical is well known to obstetricians and orthopedists.

The right ear and the right eye are more often a few millimeters, and even a centimeter, higher than the left. The two nipples are never at the same level or at the same distance from the median line. The right nipple is always a little higher. The two breasts are never at the same level, the left usually being the larger. The so-called median line, because of irregularities in the size of the two halves of the neck and the thorax, is in reality never in that position. The sculptors of the best periods of ancient Greece and Rome were apparently aware of this natural asymmetry. The heads and bodies of their statues were distinctly asymmetrical, which suggests that they modeled after living subjects rather than after some formula. The anatomists did not become aware of this fact until a century ago.

From a physiologic standpoint the most interesting asymmetries are those of the skull and face and of the preponderant right-handedness.

So far the discussion has been concerned with what may be termed normal asymmetry. It is not usually apparent and must be established by exact measurements. On the other hand, gross asymmetry, which is at once perceptible to the eye, even of any part, is rare; a decided inequality of the two halves is exceedingly rare. It is referred to in the literature as unilateral hypertrophy, hemihypertrophy, congenital hemihypertrophy, hemimacrosomia and partial gigantism. It constitutes the rarest of all developmental anomalies and has given rise to much speculation as to its etiology. The enlargement is more than hypertrophy; it really amounts to mild gigantism. In more than half the cases, along with the anomaly of growth, there are other congenital defects and degenerative stigmas, such as telangiectases, the early appearance of varicose veins, thickening of the skin, syndactylism, clubbed feet and mental defect.

4. Cox, W. C.: On the Want of Symmetry in the Length of Opposite Sides of Persons Who Have Never Been the Subject of Disease or Injury to Their Lower Extremities, Am. J. M. Sc. **69**:438, 1875.

AUTHOR'S CASE

*History.*—The patient, aged 23, was admitted to the surgical service of Cook County Hospital on Aug. 5, 1930, with a condition diagnosed as bleeding hemorrhoids. He was born in Italy. His mother had noted his asymmetry shortly after birth. There were six brothers and two sisters, all of whom did not present abnormalities. The mother and father were normal. The family history was irrelevant. The patient remembered having had scarlet fever during his childhood. At the age of 16 he had noticed varicose enlargements on the right leg. At the age of 18½ he was operated on for varicose veins of the right leg. Two years later he had noticed the appearance of new varices on the right leg and thigh. The extremity began to increase in size. At about the same time epileptic fits developed. The attacks were always nocturnal and were not accompanied

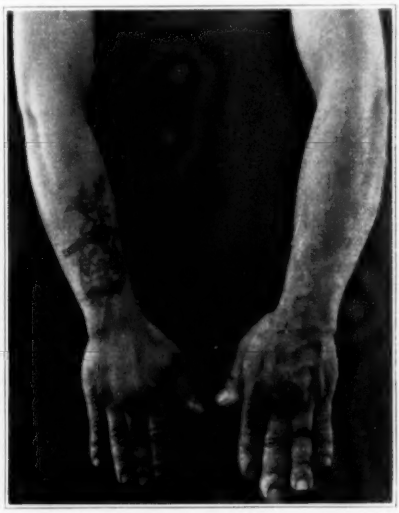

Fig. 1.—The patient's hands, showing the gigantic proportions of the left one.

by involuntary defecation or urination. His body was well developed. He was a laborer and had always enjoyed good health. He was not married, but his libido and potence were normal.

*Physical Examination.*—The patient presented a striking asymmetry, the left side being markedly larger than the right. The crown on the left side was higher, and the forehead projected further forward. The left cheek, nostril, lip and ear were larger than those of the opposite side. The median raphe of the face was displaced to the right side. The left half of the jaw was longer and more rounded and projected farther forward. The tongue consisted of a delicate right half and a much larger, thicker and longer left half. The left tonsil was larger than the right.

The left upper extremity was longer and larger than the right. The difference in the size of the two hands was striking. He could lift more with the left, though he was right-handed. The left hand, shown in figures 1 and 2, was of

Fig. 2.—Roentgenogram of the patient's hands, showing the asymmetry.

Fig. 3.—Roentgenogram of the patient's feet.

gigantic proportions. With the patient lying down, it was at once evident that the left lower extremity was longer than the right. Both feet were unusually large. The right was much thicker than the left; however, this was apparently due to edema caused by enormous varices. Examination of the accompanying photographs gives the impression that the man was formed by the union of two halves from two persons of different size and length.

In addition, a supernumerary nipple was noted 6 cm. below the right nipple. Scattered over the skin of the abdomen, both lower extremities and the entire back were small and large patches of portwine-stained telangiectases. There was

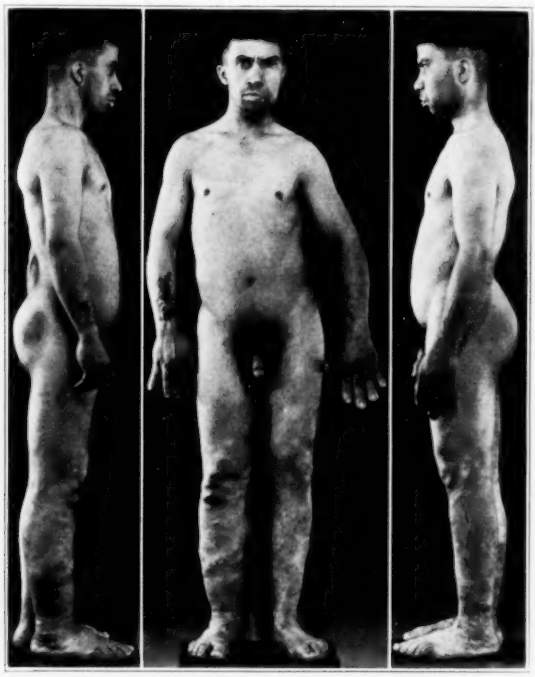

Fig. 4.—Appearance of the patient.

a long operative scar on the inner surface of the right thigh, and two longer scars on the leg. The right extremity also presented unusually large varices. The genitalia were well developed, the left scrotal sac hanging much lower than the right.

Roentgen examination of the skull revealed a perfectly normal, rather small, well outlined sella turcica with normal clinoid processes.

The blood pressure on the right side was 100 systolic and 70 diastolic; on the left, 108 systolic and 80 diastolic. The mentality was normal.

*Anthropometric Measurements.*—The upper extremities, from the tip of the acromion to the styloid process of the radius, measured: right, 52 cm.; left, 56 cm.

The circumference of the thorax at the level of the nipples measured: right half, 42 cm.; left half, 46 cm.

The lower extremities, from the superior anterior iliac spine to the inferior aspect of the internal malleolus, right, 85.5 cm.; left, 89.5 cm.

## ETIOLOGY OF CONGENITAL HEMIHYPERTROPHY

That the incidence of this anomaly is extremely rare can be seen from a survey of the literature. In 1869, Trélat and Monod,[5] in an exhaustive paper, were able to collect eleven cases. Gesell,[6] in a careful review of the literature to 1921, gathered forty cases of total hemihypertrophy. In 1927, he was able to add thirteen to this number, making a total of fifty-three cases. Analysis of these cases reveals a slight preponderance of males and a slight preference for the right side. All cases were of congenital origin, the anomaly having been noted immediately or shortly after birth. Heredity appears to have no part in the production of the anomaly; to the contrary, the absence of hereditary influences is conspicuous.

Information gained from a few postmortem examinations is more or less negative. Cagiati,[7] in a postmortem study of a typical case in a child 2½ years of age, reported the absence of any abnormality in the nervous system. The changes consisted of a hypertrophy of the connective tissues, the bones and the blood vessels of the affected side. Practically, the same findings were reported by Arnheim,[8] Hornstein[9] and Hoffman.[10] The blood vessels of the involved side were larger and showed particularly hypertrophy of the tunica media and the tunica intima. Cagiati concluded that the condition is a unilateral hypertrophy of unknown cause, involving the tissues derived from the mesenchymal layer. The enlargement of the blood vessels and the frequent occurrence of vascular abnormalities, such as nevi and telangiectasias, led some investigators to believe in a vascular origin of the disturbance. The theory is inadequate, because only about half of the cases show these vascular abnormalities, and the latter are not

5. Trélat, U., and Monod, A.: De l'hypertrophie unilatérale partielle ou totale du corps, Arch. gén. de méd. **13**:536, 1869.

6. Gesell, Arnold: Hemihypertrophy and Mental Defect, Arch. Neurol. & Psychiat. **6**:400 (Oct.) 1921; Hemihypertrophy and Twinning, Am. J. M. Sc. **173**:542, 1927.

7. Cagiati, Luigi: Klinischer und pathologischer Beitrag zum Studien der halbseitigen Hypertrophie, Deutsche Ztschr. f. Nervenh. **32**:282, 1907.

8. Arnheim, G.: Ueber einen Fall von congenitalen halbseitiger Hypertrophie mit angeborenen Bronchiectasien, Virchows Arch. f. path. Anat. **154**:300, 1898.

9. Hornstein, S.: Ein Fall von halbseitigem Riesenwuchses, Virchows Arch. f. path Anat. **133**:440, 1893.

10. Hoffman, Max: Zur Pathologie des angeborenen, partiellen Riesenwuchses, Beitr. z. klin. Chir. **43**:391, 1906.

necessarily confined to the hypertrophied side. It is more probable that the blood vessels share in the general hypertrophy.

In a case reported by Hutchison,[11] with postmortem observations by Turnbull, the latter concluded that the enlargement was caused by the obvious hypertrophy of the right suprarenal gland, the left apparently being of normal size. He also thought that the right testis was abnormally large. It is apparent that not much light has been shed by postmortem studies.

Gesell's speculations are interesting. He considered hemihypertrophy an atypical or imperfect form of twinning. By twinning is understood the production of equivalent structures by division. The tendency to bilateral equivalence, to symmetry or to mirror imaging is one of the fundamental laws in biology. Hemihypertrophy appears to be "a profound inaccuracy in the natural process of developmental duplicity." Gesell defined it as a mild unilateral gigantism of a person whose lesser somatic half is normal.

The damage or some abnormal stimulus to one half of the soma must take place early in embryonic existence. Important contributions to the solution of this biologic riddle should come from the fields of experimental embryology and teratology.

An attempt has not been made to review all the papers published or to mention all of the cases, since that has already been done. I wish, however, to add two cases to the list collected by Gesell. They have not been mentioned in any of the important contributions, because they were published under the title of "Asymmetry" and not of "Hypertrophy." I have reference to the cases of Humphrey[12] and Wachsner.[13]

25 East Washington Street.

11. Hutchison, Robert: Hemihypertrophy with Postmortem, Brit. J. Child Dis. **13**:233, 1916.

12. Humphrey, G. M.: Asymmetry of the Two Halves of the Body, J. Anat. & Physiol. **6**:226 (Nov.) 1869.

13. Wachsner, Fritz: Zur Kenntnis der bilateralen Asymmetrie des menschlichen Körpers, Berl. klin. Wchnschr. **51**:1953, 1914.

# ISOLATED CONGENITAL DEXTROCARDIA

## REPORT OF TWO CASES WITH UNUSUAL ELECTROCARDIOGRAPHIC FINDINGS; ANATOMIC, CLINICAL, ROENTGENOLOGIC AND ELECTROCARDIOGRAPHIC STUDIES OF THE CASES REPORTED IN THE LITERATURE *

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NEW YORK

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## INTRODUCTION

While cases of total situs inversus have been recognized since antiquity, isolated dextrocardia has been noted only in the past two centuries. Despite its comparative rarity, an extensive casuistic literature exists. This type of dextrocardia merits a comprehensive study, since it involves one of the most complex phases of cardiology.

The early contributions to the literature are mainly anatomic, the clinical reports being inadequate in the light of modern cardiologic methods. The roentgenographic and electrocardiographic methods of examination have added precision to the clinical diagnosis of this anomaly. The roentgenographic method permits the differentiation of the congenital from the acquired types of dextroposition of the heart,

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and total situs inversus from the isolated type. The electrocardiographic method yields information concerning the inner topography of the heart. Despite the increasing number of case reports, there are four that have been completely studied (Bahn, Pol; Plumier-Clermont; Biedermann; Rösler, Spitzer). The present study, comprising two personal observations and a critical analysis of the literature, aims to elucidate the anatomic, clinical, electrocardiographic and roentgenographic observations in this type of dextrocardia.

## DEFINITION

By the term dextrocardia should be designated only those cases in which the heart, in its own development independent of disease and anomaly in surrounding structures, assumes a position in the right side of the thorax with the apex pointing to the right. Its congenital nature is obviously assumed. "Dextroversio cordis" should, in my opinion, characterize those cases in which the displacement of the heart is dependent on a congenital or acquired extrinsic cause.* Differences in definition and contradictory concepts of the different forms of dextrocardia prevail in the literature. Nearest to the present interpretation is that of the French school (Clerc and Bobrie, Vaquez and Donzelot and others), which recognizes as dextrocardia or "dexiocardie" every primary congenital displacement of the long axis of the heart to the right, as opposed to "dextroversio cordis" applied to every acquired displacement of the heart to the right side with the apex to the left due to extracardiac causes. Vaquez and Donzelot recognized a congenital dextroversion.

The "ideal" dextrocardia is defined by Foggie as the mirror-image of the normal heart as it is found in situs inversus. The term dextrocardia is used by some German writers (Herxheimer, Mönckeberg, Pernkopf) to denote only the type associated with inversion of the chambers of the heart, while the terms "dextropositio cordis" (Pernkopf) and "dextroversio cordis" (Paltauf, Pal, Mönckeberg, Romberg, Jones, Vaquez and Donzelot and others) are reserved for the right-sided heart with normal relationship of its chambers—the former term for displacement of the heart in toto, the latter for the mirror-image displacement of its axis. The heart with normal architecture is, according to Nagel, a "genuine dextrocardia." Kundrat reserved the term, "transpositio cordis" for proved cases of transposition of the heart or

* My definition allows for Spitzer's new concept of the term "dextroversio." According to him, its characteristic is the inverse direction of the axis which is not the result of mirror-picture architecture of the heart but of gross pathologic causes. Some cases (Rösler's case 1) of "larvierte" inversion must be taken from the group of dextroversions and included in the group of dextrocardias (when the apex of the heart lies to the right).

its individual parts and "dextrocardia" for unproved cases of right-sided heart. In its broadest sense the term dextrocardia is used to include every dextroposition of the heart, acquired or congenital (Mandelstamm and Reinberg). Rösler likewise in this liberal sense stated that the term should not convey more than the information that the greater part of the heart lies in the right side of the chest.

The merit of the terms as defined by me lies in the differentiation of the primary idiopathic type from the secondary type of cardiac dextroposition on a purely embryologic basis, eliminating from the category of dextroversio cordis those cases of primary dextrocardia with normal relationship of the chambers, the mechanism of whose pathogenesis is obviously different from those dependent on extracardiac causes.

By the term "isolated" dextrocardia is meant heterotaxia of the heart alone with normal position of all other viscera (Foggie, Geoffrey St. Hilaire). Hitherto a difference in concept has existed, the term "pure" dextrocardia having been used synonymously with "isolated" (Vaquez and Donzelot, Clerc and Bobrie, Nagel, Pal). By others, "pure" has been employed to signify an "uncomplicated" mirror image dextrocardia (Blumenfeldt). Graanboom used pure in the sense of an uncomplicated isolated dextrocardia.

Dextrocardias are considered "complicated" or "uncomplicated," depending on whether cardiac malformations accompany the anomalous position of the heart. The proposal to limit the term "isolated" to "uncomplicated pure" cases (Clerc and Bobrie, Vaquez and Donzelot) is not warranted.

## REPORT OF CASES PERSONALLY OBSERVED

Case 1.—*History.*—T. R., aged 19 years, single, a telephone operator, was admitted to the Mount Sinai Hospital on May 25, 1928, to the dermatological service of Dr. Hermann Goldenberg, who gave me permission to report the case. The presence of the dextrocardia was discovered by the ward physician, Dr. L. R. Tuchman, in the course of a routine examination. The patient had been referred to the hospital for the treatment of an eruption on her face and arms of three years' duration. Her father was alive and well; her mother died of influenza in 1918. A sister and brother were well. So far as she knew, no member of her family suffered from cardiac trouble or anomaly of the position of the heart. There was no history of consanguineous marriage in the family. As a child she suffered from scarlet fever and measles. Six years before admission to the hospital, her tonsils were removed. There was no previous history of pleurisy or pneumonia. She had frequent colds in the winter. One year before admission, she lost her voice for six months due to laryngitis. She had never had hemoptysis. She had frequent headaches at the end of the working day. At the age of 4, she became aware that her heart beat on the right side. At the age of 8, she was restricted in her activities because of pain in the cardiac region on exertion. Cyanosis was not noticed at this time, but the fingers sometimes became blue; the lips were not noted. Ordinarily she had slight dyspnea on exertion. There was no history of rheumatic fever, pains in the muscles and joints or chorea.

There had never been any swelling of the lower extremities. The menses, which began at 13, were regular with no dysmenorrhea. The patient was moderately obstipated. Three years before admission, an eruption appeared on the dorsum of the right arm up to the level of the elbow. Despite topical and roentgen treatment for a year and a half, the lesion persisted. Then the face became involved, especially the cheeks, forehead and ears. The lesions were better in summer than in winter.

*Physical Examination.*—The stature and weight of the patient were normal for her age. On her face were impetiginous areas, crusted over with yellowish exudate and with an inflammatory reddened base. The forehead was covered with lesions similar to those of the face except that there was less exudate. The lips were reddish in color, not blue or pale. There was no adenopathy. Intranasal examination indicated the presence of bilateral disease of the ethmoid. Examination of the lungs revealed no abnormalities. There were no râles at the bases of the lungs.

Heart: The apex beat was in the fifth intercostal space, 6 cm. to the right of the midline. The right border of cardiac fulness was 3 cm. to the right of the midline in the second space, 5 cm. in the third space and 5 cm. in the fourth space. The left border was inside the left sternal margin in the second and third intercostal spaces and just to the left of the sternal margin in the fourth intercostal space. The heart sounds were of good quality. There was a short rasping systolic murmur heard over the entire precordium. No thrill was felt. There was a pulsation systolic in time in the third and fourth right intercostal spaces near the sternum. There was a rough systolic murmur in this area especially, besides the one over the apical region. The second sound was short and snapping. The cardiac sounds were also audible to the left of the sternum, but they were not as loud.

Examination of the extremities showed moderate clubbing of the fingers. There was no cyanosis and no edema of the extremities.

Abdomen: The liver was not palpable. There was dulness in the right hypochondriac region. A tympanitic note was heard in the left upper quadrant. The abdominal aorta pulsated to the left of the vertebral column.

Skeletal: There was slight scoliosis of the thoracic spine.

*Laboratory Examination.*—The Wassermann reaction of the blood was negative. Analysis of the blood showed: urea, 13 mg.; cholesterol, 160 mg., and sugar, 73 mg. per hundred cubic centimeters of blood. The basal metabolic rate was minus 12 and minus 15 per cent.

*Roentgenographic Examination.*—Fluoroscopy was done on Nov. 30, 1928. The right border of the heart was rounded, but the apex was not definitely found. The aortic arch was partially to the left of the sternum. The retrocardiac space was seen in the second oblique position. The arch of the aorta was visualized in the right first oblique position, corroborated in the posterior anterior view. The liver and stomach were in their usual position (fluid level and carbon dioxide inflation by compound effervescing powder, U. S. P.).

X-Ray Plate of Chest: The heart (fig. 1) was completely transposed to the right side of the chest. The right border of the heart was rounded. There was no abnormality in the thoracic wall, other viscera or the pulmonary fields to account for the abnormal position of the heart. The aortic arch crossed the left bronchus. The right leaf of the diaphragm was lower than the left.

*Electrocardiographic Examination.*—The tracing (fig. 2) showed a very low P wave inversion of the T wave and an upright QRS complex in lead I. T2 was

slightly inverted. Leads II and III were not interchanged. There was no ventricular predominance. There was normal sinus rhythm.

*Diagnosis.*—Isolated mirror-picture dextrocardia; defect of the interventricular septum; generalized neurodermatitis and bilateral ethmoiditis were diagnosed.

*Course.*—The patient continues to work as a telephone operator and has been well except for the condition of her skin, for the treatment of which she returned to the hospital in June, 1929. At that time the foregoing diagnosis were reaffirmed. The cardiac symptoms remained unchanged.

*Comment.*—The congenital nature of this case is beyond doubt; the dextrocardia was recognized at the age of 4, and some transitory limi-

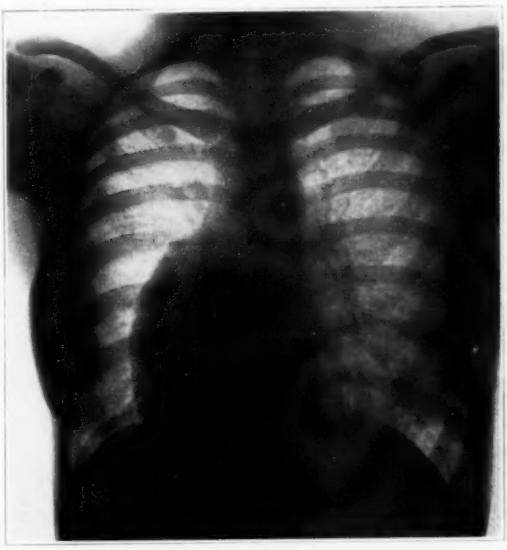

Fig. 1 (case 1).—Roentgenogram of chest showing position of the heart.

tation of physical activities at the age of 9 due to cardiac symptoms. The patient now works and lives a normal life. The dextrocardia was recognized incidentally, the patient seeking relief for a cutaneous disease. The associated cardiac malformation is likewise undoubtedly congenital in nature. The absence of frank cyanosis and a thrill argue against the presence of a pulmonary stenosis. The aorta crosses the left bronchus and descends on the left side of the vertebral column. The abdominal organs occupy their normal position. The roentgenogram of the chest shows clear, pulmonary fields. The right leaf of the diaphragm is lower than the left. The very low P wave and the inversion of the T wave in the first lead of the electrocardiogram suggests the possibility of inversion of the chambers of the heart. The upright QRS

complex in lead I would indicate that the greatly hypertrophied transposed "right" ventricle, now on the left side, distorted the electrocardiogram. This view is supported by the electrocardiographic and anatomic evidence in the case of Abbott and Moffatt, the electrocardiogram and roentgenogram of which are here reproduced (figs. 3 and 4). In this case a mirror-picture dextrocardia occurring in a partial heterotaxia was found, and was diagnosed intra vitam by the roentgenogram and the electrocardiogram. The P and T waves in lead I were inverted, and the QRS was upright instead of the familiar inversion of all the

Fig. 2 (case 1).—Leads I, II, III from above downward.

main deflections always found in this lead in cases of uncomplicated mirror-picture dextrocardia. Anatomically, a markedly hypertrophied transposed "right" ventricle and an aplastic transposed "left" ventricle were found. My case, that of Abbott and Moffatt, the following case and other cases to be cited subsequently (cases under "Unusual Findings in Dextrocardia," second installment of article) stress a new phase of the interpretation of the electrocardiogram in cardiac conditions associated with simultaneous displacement of the cardiac axis, alteration of the inner topography of the heart and cardiac malformation and disease.

Case 2.—*History.*—A. H., aged 43, married, an upholsterer, was admitted to the outpatient department of the Mount Sinai Hospital on Oct. 17, 1927, where I observed him. He complained of pain on urination and occasionally inability to

pass urine. He had a daughter 19 years old (right-handed) and another 6 years old (left-handed); both were well, and were not known to have malposition of the heart. A son of 14 years (right-handed) was found to have a normally situated heart. The patient's wife was well, and her heart was in its normal position. There was no family history of consanguineous marriage. The patient suffered the usual diseases of childhood. There was no history of pleurisy or pneumonia. He always enjoyed good health. Three years before admission, he had attacks of pain in the left loin. He was unable to pass urine and had to be catheterized. He had never had influenza. He had never noted or been informed by a physician of displacement of his heart. He was a heavy smoker and did not drink alcoholic beverages. For three years before admission he had had a cough now and then,

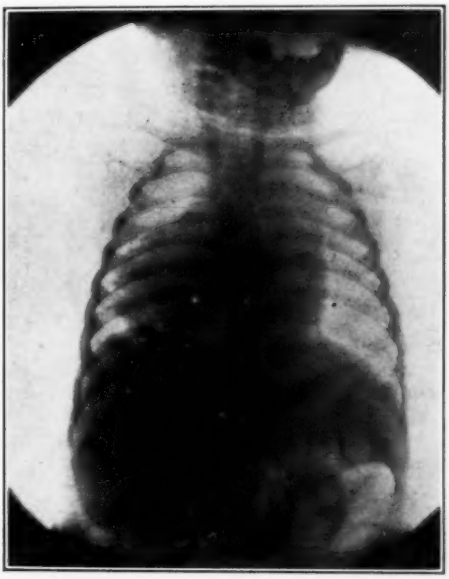

Fig. 3.—Roentgenogram of chest in Abbott and Moffatt's case 2. (Published for the first time, with permission of the authors.)

with dark scant expectoration, occasionally blood-streaked. He had noticed shortness of breath on walking rapidly or climbing stairs. At no time had he suffered an attack of syncope. Three weeks before admission he again noted difficulty in urination accompanied by an attack of severe pain in the left side. He was catheterized. The urine contained blood. He passed small amounts of urine containing blood with great pain.

*Physical Examination.*—The patient was a robust man of medium height weighing 177 pounds (80.3 Kg.). He had a peculiar pallor, but no evidence of cyanosis. His eyes reacted to light and accommodation. The tonsils were markedly hypertrophied. His neck was short and stout. He was hyposensitive to pain (Libman's test). He was right-handed.

Chest: The thorax was symmetrical; resonance was normal throughout. Tactile fremitus was more marked over the right side of the chest. The expiratory phase of respiration was prolonged. There were numerous musical râles throughout both sides of the chest. There were no moist râles to be heard at both pulmonary bases.

Heart: An area of pulsation was visible in the right sixth intercostal space 10 cm. from the midline, and the apex beat was palpable in this region. There was no pulsation visible in the left side of the thorax. On percussion, the heart was found to be enlarged. The major portion of the area of cardiac dulness was in the right side of the chest, although a portion of the heart was found to the

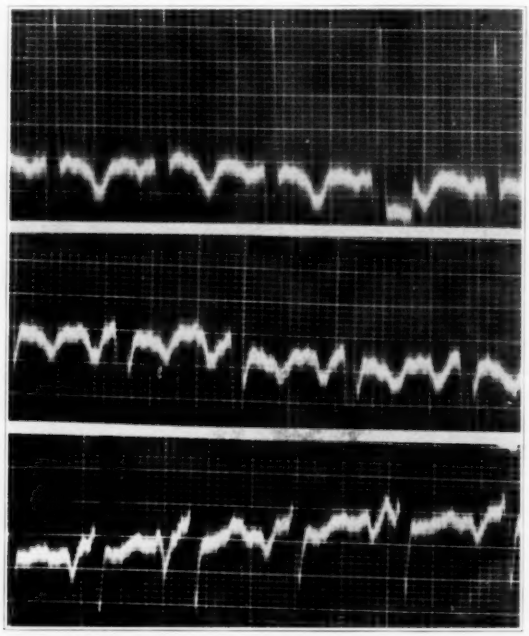

Fig. 4.—Electrocardiogram in case 2 of Abbott and Moffatt. Lead I, P and T inverted, upright; "Q" unusually deep; leads II, P and T inverted, upright; "Q" unusually deep; lead III, P diphasic, upright, T upright, rhythm regular; normal conduction. At necropsy, a markedly hypertrophied transposed "right" ventricle and an aplastic transposed "left" ventricle were found. (Published for the first time, with permission of the authors.)

left of the sternum. In the second intercostal space, the heart percussed 6 cm. to the right and left of the midsternal line; in the third, 8 cm. to the right and 7 cm. to the left; in the fourth, 10 cm. to the right and 7 cm. to the left, and in the sixth intercostal space 13 cm. to the right of the midline. Below, the area of cardiac dulness was continuous with the area of hepatic dulness.

The heart sounds were best heard in the right fifth and sixth spaces, although they were also heard faintly in the same spaces just to the left of the sternum. A

soft systolic murmur was heard in the fifth and sixth spaces to the right and left of the sternum. There was no palpable thrill. The second sound in the second right intercostal space was louder than that in the corresponding second left intercostal space. When the patient was shifted, the area of cardiac dulness moved to the right or left.

The radial pulse was regular, the rate varying between 45 and 58 beats per minute on five different examinations. There was no deficit of the pulse. In the right arm, the blood pressure was 135 systolic and 80 diastolic, and in the left, 125 systolic and 60 diastolic. There was only slight clubbing of the fingers.

Abdomen: The liver was palpable one fingerbreadth below the right costal margin. The abdominal aorta was not palpable. The left testicle was lower than the right.

*Laboratory Examinations.*—Urinalysis showed the presence of albumin, numerous red blood cells, a moderate number of white blood cells and an occasional hyaline cast. The sputum contained no tubercle bacilli.

*Roentgenographic Examination.*—Fluoroscopy was done. The examination of the chest was interpreted as follows: The two main cardiac contours were the ventricles in their normal relationship, except that the right was huge and the left hypoplastic; the aorta was anomalous and small; the pulsations of the right and left cardiac borders were synchronous and regular; the auricles could not be identified (important in view of the presence of auricular fibrillation). The esophagus as outlined by barium sulphate appeared to be in its normal position and relation to the aorta (persistent right aortic arch ruled out). In the right oblique position, the retrocardiac space was not visualized; in the left oblique, it was, although in this view the arch of the aorta could not be definitely outlined. The arch of the aorta was not visualized in the right oblique position either. A vertical shadow above the left contour of the heart was considered as the descending aorta. A shadow at the left leaf of the diaphragm adjoining the left cardiac border was not visualized. The diaphragm moved freely, the right leaf being definitely lower than the left. A barium sulphate meal showed the stomach and duodenum to be normal in position. The liver was in its normal position.

X-Ray Plate: A teleoroentgenogram (fig. 5) showed the heart to be enlarged and to be situated almost entirely in the right side of the thorax except for a small portion to the left. In contour, the heart was in mirror-image position to what it would be in the normal subject with definite hypertrophy of the ventricle represented by the right main cardiac contour and that portion immediately above, which in a transposed normal heart would represent the left auricle. The pulmonary artery was now visualized. The arch of the aorta crossed the left bronchus and descended on the left side of the vertebral column. There were some infiltrations in both bases of the lungs probably due to long-standing congestion or bronchiectasis. Dr. Harry Wessler assisted in the interpretation of the roentgenogram. Examination of the urinary tract showed the presence of calculi in the region of both kidneys and one in the lower end of the left ureter about 2 inches above the vesical orifice.

*Electrocardiographic Examination.*—The electrocardiogram (fig. 6) showed ventricular rates of 45, 55 and 52, respectively Nov. 2, 1927; Dec. 15, 1927, and May 16, 1930, regular in leads I and II and slightly irregular in III. Auricular fibrillation was noted. In lead I, QRS was upright and T inverted. QRS in leads II and III was upright. The T waves were opposite the main deflections in all leads (ventricular complexes were large and diphasic). The QRS interval mea-

sured 0.12 of a second. Leads II and III were not interchanged. Drs. B. S. Oppenheimer, M. A. Rothschild, Hubert Mann and I. R. Roth aided in the interpretation of the electrocardiogram.

*Polygraphic Tracing.*—The polygram made by Dr. Hermann Mond showed a venous pulse characteristic of auricular fibrillation. The A wave was missing, and a number of small irregular waves were visualized, "fibrillation waves." The systolic collapse of the vein was well marked. There was no sign of a tricuspid lesion. The arterial pulse showed no abnormality.

*Diagnosis.*—Dextrocardia without situs inversus of the ventricles, interventricular septal defect, anomalous position of the great vessels with normal relationship to respective ventricles, auricular fibrillation, congenital complete heart block,

Fig. 5 (case 2).—Roentgenogram of chest showing position of the heart.

bradycardia (idioventricular rhythm), bronchiectasis (?) and renal and ureteral (left) calculi were diagnosed.

*Course.*—The patient has been under observation for two years, during which time there has been no change in his physical condition. He works regularly and strenuously. The cardiac symptoms remain unchanged. There is no evidence of cyanosis or increasing shortness of breath.

*Comment.*—The interpretation of case 2 involves a more difficult problem. While the dextrocardia was recognized late in life, no etiologic factor can be found to explain the dextroposition other than its congenital nature. The absence of cyanosis, the age and physical examination of the patient would indicate that the associated malformation does

not seriously affect the physiology of the heart. Roentgenographic examination shows no cause of traction or of displacement of the heart. The right leaf of the diaphragm is lower than the left; the abdominal organs are in their normal position. In this case as in case 1, the cardiac symptoms were incidental, the patient seeking relief for renal colic. This patient also carries on his occupation, which is strenuous. The roentgenographic evidence of long-standing congestion of the lungs, the symptom-free auricular fibrillation recognized by the electrocardiogram and the venous tracing, a persistent bradycardia without spontaneous syncopal crises and electrocardiographic evidence of complete heart block and idioventricular rhythm with no history of an episode pointing to

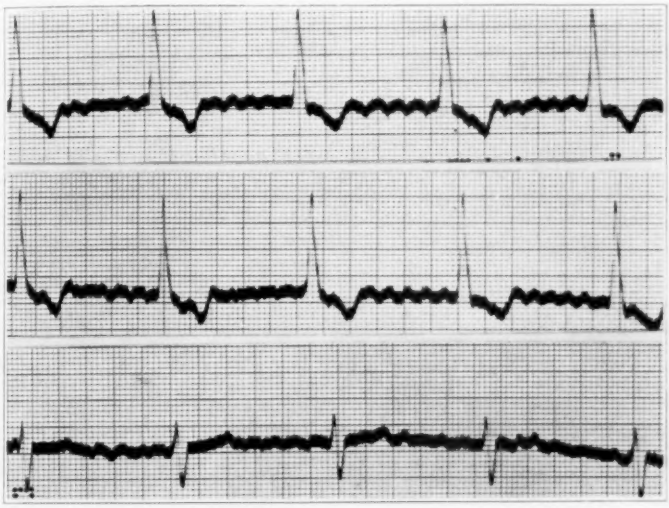

Fig. 6 (case 2).—Leads I, II, III, from above downward.

disease of the coronary artery in a man only 43 years old with dextrocardia would suggest that the electrocardiographic evidence of both auricular fibrillation and conduction defect are more logically explained as the results of a congenital lesion than an acquired lesion on the basis of disease of the coronary artery.

The persistent regular bradycardia in the presence of auricular fibrillation points to the presence of a block in the main stem of the bundle of His probably associated with the septal defect.

The occurrence of partial heart block in association with congenital cardiac disease, especially defects of the septal and auriculoventricular nodes, was reported by Wilson and Grant (1925) in a child of 14 months in whom pulmonary atresia and complete absence of the interventricular

septum was found. They found in the literature 17 clinical cases of complete and partial heart block of congenital origin and in another case the condition was found post mortem (Storch). The observations of Keith, Mönckeberg, Carter and Howland, and Romberg and White indicate that the position of the auriculoventricular bundle on the upper border of the interventricular septum or on the posterior wall of the heart, respectively, is the usual one in hearts in which the septum is partially or totally deficient. In the heart described by Mann and examined microscopically by Mönckeberg, the auriculoventricular system was found on the surface of a muscular prominence on the posterior wall of the common ventricle (case of cor trilocular biatrium) as in Wilson and Grant's case. Additional cases of congenital origin have been recorded recently by Aylward (2 cases), and Lampard, Fleming and Stevenson (1928) reported 2 cases, 1 partial and the other complete with patent intraventricular septum and malformation of the auriculoventricular bundle.

Josué described a case of pulmonary stenosis with intraventricular communication and "allodromie" due to destruction of the terminal left branch of the bundle of His. The electrocardiogram showed delayed conduction, notching of $R_{III}$ opposite deflection of T in leads I and III (upward in I, downward in III) and right ventricular predominance. He maintained (concurring with observations of Keith, Sapegno, Mönckeberg, Laubry and Pezzi, and Marcel L'Abbe) that the interference in conduction is due to secondary inflammatory or degenerative processes engrafted on the margins of the septal defects, the resultant fibrous tissue causing pressure on the bundle or its branches, or the inflammatory process destroying them.

The auriculoventricular conduction system is normal in cases with defects of the subaortic septum and persistent total truncus. The extremely rare congenital anomalies of the conduction system per se are displacement of the sinus node, abnormal course of the auriculoventricular conduction system or abnormal neighboring relations (Mönckeberg). Morrison's case showed a blind ending of the left branch and hypertrophy of the right branch of the bundle of His. In Sato's case there was transposition of both branches of the conduction system with normal position of auricles and transposition of the venous ostia.

Laubry cited a case seen with Mougeot in a man 60 years of age, with bradycardia and complete dissociation of conduction between auricle and ventricle, in whom a latent defect of the interventricular septum was found at postmortem examination. This lesion was interpreted as a point of departure of inflammatory lesions that caused destruction of the bundle.

The regularity and the large diphasic form of the ventricular complexes, and the slightly prolonged conduction time over a period of observation of two and one-half years in the presence of auricular fibrillation, suggest that the ventricles in my second case are activated by an idioventricular center. In form, the ventricular complexes suggest a bundle branch block of the common type. The present controversy as to the types of bundle branch lesions (Wilson and his co-workers), the presence of dextrocardia and the lack of positive evidence as to the relation of the chambers of the heart due to the unusual electrocardiogram, make it hazardous to interpret the location of the idioventricular rhythm and the question of ventricular predominance.

In a case of complete situs inversus, Potts and Ashman encountered similar considerations with the exception that they were definitely dealing with a mirror-picture heart. The electrocardiogram showed "right ventricular predominance, ventricular ectopic beats and retrograde conduction." The diagnosis of partial left (functional right) bundle branch block was entertained but not favored because of the observations of Wilson and Hermann that the QRS complex varies with the cardiac rate in the presence of partial bundle branch block and auricular fibrillation, and the right ventricular predominance attributed in the absence of any cardiac hypertrophy to the rotation of the heart around its longitudinal axis.

In Meyer's case, studied by the roentgenogram and the electrocardiogram, complete heart block was accompanied by complete cardiovisceral transposition, pulmonary stenosis and defect of the interventricular septum. In lead I of this case, P and T were inverted, R only slightly; S was highly upright (left ventricular predominance) and leads II and III replaced each other. This case, that of Abbott and Moffatt, and my cases show beyond doubt the expression in the electrocardiogram of the combined influence of axis deviation and direction of electrical potential of situs inversus, right ventricular hypertrophy and conduction defects associated with congenital cardiac disease or malformation.

My second case and that of Krestin are the only cases of isolated dextrocardia associated with auricular fibrillation. The latter case is attributed to an acquired mitral stenosis. In my case the auricular fibrillation cannot be explained on the basis of a congenital lesion but possibly as the result of a long-standing (congenital) heart block.

In the absence of confirmatory evidence in the electrocardiogram, my diagnosis of dextrocardia with normally related ventricles rests entirely on the interpretation of the roentgenogram. In my opinion, it is the right ventricle that is hypertrophied and in the presence of situs inversus of the ventricles would not give the cardiac contour observed here.

## HISTORY OF THE SUBJECT

Severinus of Rome (1643) first noted dextrocardia in complete situs inversus. Soon after, the first anatomic case of a dextrocardia occurring in a partial heterotaxia was recognized by Moellenbrock and Hoffmann. Senac, in 1749, divided cases of dextrocardia into acquired and congenital types. Eschenbach (1769) described a case of isolated dextrocardia with transposition of the aorta, including its abdominal portion, recorded in Ferrein's Anatomy (1741) (vide Aufermauer citing Gruber; Krieger). Geoffrey St. Hilaire (1832) collected 60 cases of dextrocardia, 30 of which were not accompanied by transposition of other organs (cf. Falck). Boillaud (1835) (cf. Krieger) first recognized isolated dextrocardia clinically and differentiated between displacement and transposition of the heart. DeBeauvais [37] pointed out the importance of differentiating the isolated form from complete situs inversus. Mosler (1866), Schroetter (1870) and Pope (1882) gave early clinical descriptions. The first roentgenographic observation of an isolated dextrocardia was made by Vehsemeyer. Stoerk (1911) made the first electrocardiographic study of a case of dextrocardia (Rösler), but the first detailed electrocardiographic record was made by Moffett and Neuhof (1915) in an isolated dextrocardia with inversion of the chambers. Weinberger believed his 2 cases to be the first isolated cases with inversion of the chambers to be studied by electrocardiograms. Anderson described anatomically isolated dextrocardia occurring in a mouse.

## GENERAL CONSIDERATIONS

### ETIOLOGY

The familial incidence of dextrocardia in complete situs inversus has been noted in twins (Reinhardt), two brothers (Löwenthal, Ochsenius, Reid, Carpenter), three brothers (Carpenter), brother and sister (Curschmann, Neuhof), two children in one family, sex not given (Fröhlich) and in four generations (Lancisi). Familial incidence has also been noted by Rogi, Leroux, Labbé and Barret, Baumann, Liotta and Bianchi. In isolated dextrocardia, the familial incidence has been denied by Clerc and Bobrie and Mandelstamm and Reinberg. The only instances I find are that of Doolittle, in father and son in a family with two generations of twins, and that of Boruttau and Stadelmann in a maternal uncle.

The incidence of twins in families with dextrocardia is confined to these cases of Doolittle, Reinhardt, MacLennan and Schott; Schmilinsky and Nagel referred to 2 cases in a series of 24 isolated dextrocardias. A family history of cardiac disease is reported by Bahn in his case and in 5 other instances (Baumgarth, Mosler, Sussmann, Neumann, Gruss). Nagel also referred to 5 instances. Rösler noted this in his first case

and emphasized consanguineous marriage in relation to congenital cardiac disease. Abrahamson noted a family history of rheumatic fever in a case of total situs inversus (case 3). In my series a family history of cardiac disease was found in 9 cases and of rheumatic fever in 3 cases. A history of acute articular rheumatism was given in 6 cases.

The age incidence studied by Clerc and Bobrie in 57 cases of isolated dextrocardia was found to be 6 persons under 1 year, 12 in the first decade of life, 12 in the second, 13 in the third, 2 in the fourth and 3 older than 50 years (63 years, Pope and Lucchi; 67, Giovannini). In Rösler's collection of 24 cases that came to necropsy, there were 11 in the first year of life, 4 in the first decade of life, 2 in the second, 1 in the third, 3 in the fourth, 2 in the fifth, none in the sixth and 1 in the seventh; the average age was 14 years. In his series of 127 clinical cases, the average age was 23½ years with the following age incidence: first year of life, 5 cases; first decade, 26; second, 28; third, 28; fourth, 18; fifth, 5; sixth, 7; seventh, 1, and eighth, 1. In my entire series of 144 cases with age given, in the first year of life there were 17 cases; in the first decade, 31; in the second, 24; in the third, 30; in the fourth, 21; in the fifth, 12; in the sixth, 5; in the seventh, 3, and in the eighth, 1.

There were 42 males in Clerc and Bobrie's series of 56 cases. In Nagel's collection of 24 cases, 16 occurred in males and 4 in females; in 3 cases the sex was not given. In Rösler's collection of 24 anatomic cases, 10 were in males, 10 in females and in 4 cases the sex was not given. In my series, in those cases in which sex is mentioned, 89 were in males and 51 in females. In the cases verified by necropsy, the ratio of sexes is 1:1; in the clinical series it is approximately 2:1, which is the ratio given by Kuchenmeister for cases of complete situs inversus. Baumann attributed this apparent predominance in males to the fact that many of the reported cases were found in army recruits, and that the breasts of women make the detection of dextrocardia improbable on casual examination.

Congenital skeletal deformities associated with accepted cases of dextrocardia have been reported by Tison (thirteen ribs on the right side, eleven on the left, sixth and seventh fused); by Henoch, in a case of isolated dextrocardia (absence of radius and left thumb); by Wagner (total hemiatrophy of the right side of the face); by Mandelstamm and Reinberg (case 7b, isolated dextrocardia with fissure of sternum, and a case of complete situs inversus in a boy of 17 with a supernumerary sixth finger and accessory cervical mammae); by Grünfeld (congenital umbilical hernia); by Moffett and Neuhof (metacarpal deformities); by Rösler (case 3, finger defects, syndactylism of toes, cervical rib, fissure of sternum) and by Sakurai in a case of partial heterotaxia (harelip and cleft palate).

Intra-uterine traumatism or disease as a factor in the causation of dextroposition has been emphasized by Berwald, Pic and Alaux, and also by Cade, Rebattu and Gras in whose case an early pleurisy, which later disappeared, presumably caused the right-sided heart. In Berwald's case, incorrectly reported as a genuine case of pure congenital dextrocardia, the left pectoral muscle was absent and the left ribs depressed at the sternum. At necropsy, the pericardium was found adherent to the wall of the chest, and the apex pointed to the left. The anomaly in this case must be attributed to intra-uterine traumatism. (For a series of similar cases of "Rechtslage" of the heart associated with defects of the rib, muscle and sternum see "Cases of Congenital Dextroversion" under "Special Lists of Cases," second installment.) Uterine fibroids may press on the growing fetus and cause such deformities. Transitory traumatism may alter the position of the heart without leaving a trace of deformity of the thorax owing to the elasticity of the growing thoracic wall.

In cases of complete situs inversus, left-handedness has been noted in from 48 to 50 per cent (Scandola) and in 23 of 31 cases (Ebstein). In LeWald's series of 28 cases of complete situs inversus and 1 of isolated dextrocardia, all of the patients were right-handed. Weygandt considered left-handedness as evidence of a partial situs inversus with transposition of the cerebral hemispheres. Among the cases of isolated dextrocardia, right-handedness is the rule, but left-handedness has been noted by Sobiercyzk and by Vehsemeyer, by Nagel in 3 of 5 cases and by Bonheim in his case; Mandelstamm and Reinberg noted no case in a series of 5 of 7 cases of isolated dextrocardia in which mention is made of dexterity and 3 with a history of left-handedness in a series of 26 cases of total situs inversus. In my series, left-handedness occurred in 5 of 15 cases in which this point was noted.

The lower position of the right testicle is a more dependable sign of heterotaxia than left-handedness. Ebstein observed the right testicle to be lower in 28 of 36 cases of complete situs inversus; Mandelstamm and Reinberg, in 6 of 9 men with total situs inversus, and Royer and Wilson, in a case of incomplete heterotaxia. In my second case, the testicles were in normal position.

The frequency of cases of isolated dextrocardia reported by different authors vary according to their definition and their discrimination of suitable cases:

Breschet, 1826: Ill defined group of anatomic cases mainly of the acquired type; 1 case of isolated dextrocardia

Schroetter, 1870: Ill defined

Krieger, 1880: 16 cases, presumably isolated but not well defined

Vehsemeyer, 1897: 27 cases

Aufdermauer, 1907: 55 cases

Nagel, 1909: 23 cases from the German literature; 16, clinical only

Herxheimer, 1910: 40 cases, 17 with necropsy

Foggie, 1910: 46 cases, clinical only; 7, necropsy only; 5, clinical and necropsy, with a sixth personal case

Moffett and Neuhof, 1915: 124 cases, but obviously not all isolated as claimed

Clerc and Bobrie, 1918: 50 cases, clinical only; 11, post mortem; 23 of 55, complicated (collection too large, in spite of care claimed in selection)

Laubry and Pezzi, 1921: 60 cases including 1 personal case; 29 with necropsy

Mandelstamm and Reinberg, 1928: 7 additional personal cases

Rösler, 1930: 24 cases with necropsy; 127 cases of "Rechtslage" of the heart; some cases of congenital dextroversion included; 7 personal cases added to literature

Lichtman, 1931: 10 cases, necropsy only; 26 cases, clinical and necropsy; 125 cases, clinical only; 2 personal cases added

## GENESIS OF ISOLATED DEXTROCARDIA

A review of the literature indicates that little progress has been made in the knowledge of the real cause of this anomaly. The numerous theories advanced to explain the cause of total situs inversus may be briefly alluded to: turning of the embryo itself (Baer, Remak, Bischoff, B. S. Schultze), primary turning of the cardiac tube (Dareste), twisting of the umbilical cord to the left in the fetus (Virchow), persistence of the right omphalomesenteric and umbilical veins instead of the left (Lochte) and the twin theory of Schott and Forster, (reviewed by Nagel, Paltauf, Reinberg, Fulchiero, Aufdermauer, Mandelstamm and Reinberg, Laubry and Pezzi and others).

The mechanism of the isolated type of dextrocardia must necessarily be even less understood, especially since many variations are involved. Rindfleisch explained partial heterotaxia as due to the physical mechanism of the altered flow of the blood column. Marchand showed long ago that the reasons for the development and existence of total and partial situs inversus differ from each other markedly, and that these conditions owe their origin to different factors.

However, it may be stated with some certainty that chronologically the dextrocardia of total situs inversus occurs in the earliest phase of the development of the embryo not later than the tenth to the fifteenth day after fertilization of the ovum, when the S-shaped curve of the primary embryonal heart tube takes place (Herxheimer, Mönckeberg); at this time, a contrasigmoid turning of the cardiac tube occurs instead of the usual sigmoid twist.

By a careful and systematic investigation of the anatomic material in cases of partial heterotaxia, such as Pernkopf has made, interesting data pertaining to the concept of the genesis of the different types of dextrocardia have been obtained. The contention of Lochte that transposition of isolated organs in one body cavity cannot occur in associa-

tion with a normal relationship in the other is disproved. Pernkopf demonstrated that different organs or organ complexes or parts thereof may develop a mirror-image position, and that the anlage of an organ in the sense of its normal or inverse symmetry exerts no influence on the development of the form or position of an adjacent organ. It is his opinion that the diffrent components of the embryonic heart may develop in an independent manner and unrelated to one another in the sense of a situs inversus. A situs solitus of a single organ has been observed in spite of a general situs inversus. Cases of complete situs inversus with sinistrocardia must be considered as instances (Hickman and others).

The time of incidence of the isolated inversions of the entire cardiac organ complex or individual parts must also occur as early in embryonic development as they do in complete situs inversus. According to Spitzer, total situs inversus and partial situs inversus are fundamentally identical in genesis (Marchand and Lochte believe they differ, the latter occurring later in embryologic development). According to him, they represent the contrary to the normal phylogenetically developed organ. The isolated inversions correspond to inversion of the primary genetic divisions of the anlage of the heart, the sinus, the primary atrial, the primary ventricular or bulbus metameres or the entire cardiac metameric complex. The malformation usually associated with isolated cardiac inversion must necessarily occur because anatomic and functional continuity is maintained despite the fact that correlated portions of the heart do not undergo simultaneous inversion. The rules governing the transposition of the bulbus metamere differ from the rest of the cardiac complex.

It is Spitzer's concept that transposition of the vessels is a result of a combination of recent and atavistic phylogenetic and ontogenetic influences on the development of the bulbus metamere. In his opinion, in the evolution of the lung-breathing terrestial species from the aquatic gill-breathing types, the pulmonary portion of the cardiac tubes assumed a rôle as important as the systemic portion with a consequent development of both these systems side by side separated by septums. In order, however, that aerated blood may reach the systemic circulation, a complete torsion through an angle of 180 degrees of the arterial end must take place, so that aerated pulmonary blood may go to the left side of the heart and be discharged therefrom, and nonaerated systemic blood may go to the right side of the heart and be discharged into the lungs. That such a rotation occurs is seen in the clockwise spiral of the aortopulmonary septum. Thus in the definitive heart, as the pulmonic trunk descends it swings from behind the aorta around to the left and anteriorly, reversing proximally its distal relationship to the

aortic trunk. When the vascular growth of the fetus is impaired, the development of the pulmonic side of the heart and the septums is usually interfered with, and so-called "detorsion defects" occur. There is a complete absence of the 180 degrees spiral rotation of the arterial end or only to a variable degree, resulting in the different types of transposition of the great vessels. This underlying detorsion at the arterial end of the cardiac tube does not entail any countertorsion at the venous end of the heart. A group of cases of dextrocardia without inversion of the chambers with anomalies of the great vessels may be considered as mechanically the result of detorsion defects (cf. Paltauf, Lochte, Shapiro's case 1). A group of cases of dextrocardia with inversion of the ventricles with so-called "corrected transposition" of the great vessels (Lochte, Paltauf) and so-called dextroversion with transposition of the great vessels may be explained as the opposite in genesis teleologically of the two anomalies, the transposition of the vessels and the inversion of the chambers (Rösler and Spitzer's case). The dextrocardia associated with persistent right aortic arch may similarly be explained on a mechanical basis.

The second type of isolated dextrocardia without inversion of the chambers is considered by Nagel to be due to an arrest of development occurring in the teratogenetic-termination period of about the sixth week. At this time the normal heart fully developed occupies a median position in the thorax almost symmetrically perpendicular to the long axis of the body, with slight preponderance of the right ventricle. At this point the heart fails to rotate to the left as normally and rotates with its apex to the right with a slight degree of torsion of the vascular pedicle.*

The preponderance of the right ventricle is probably an important but not the sole factor in the pathogenesis of this type. Truly most of these cases have right-sided congenital malformations but so do cases of congenital cardiac disease without dextrocardia. Furthermore, there are cases of dextrocardia of this type without malformations (Pope, Lucchi, Wendling). The higher blood pressure and the normal overgrowth of the left ventricle may account for the normal deflection of the heart to the left. Paltauf believed the upward growth of the predominant right lobe of the liver or a transient fetal hydropericardium

* A group of borderline cases designated as "mesocardias" belongs here. I must insist for acceptance under the heading of true dextrocardia that the apex lie to the right. Gorter erroneously implies that in isolated dextrocardia the apex lies to the left. Cases of median heart erroneously reported as dextrocardia follow: anatomically verified, Sandifort, Wilson, Otto, Breschet, Kussmaul, Pernkopf's case 4; clinical only, Schroetter, Stone, Hochsinger (roentgenogram), Gorter (roentgenogram).

to be responsible for the normal turning of the heart to the left. Broman, concurring, expressed the belief that the right lobe of the liver growing cranialward meets the heart in descent, diverting it to the left. An abnormally large left lobe of the liver has been considered the cause of the turning of the apex of the heart to the right (Shapiro's case 1).

The occurrence of three uncomplicated cases of dextrocardia without inversion of the chambers nullifies the contention of Paltauf and of Kundrat that a normal heart cannot occur in dextrocardia because it would result in kinking of the great vessels. Clerc and Bobrie maintained that these uncomplicated cases prove the later intra-uterine development of this type since a normal heart and blood vessels have already been formed. They also disprove the theory that the associated malformations are the result of the dextrocardia. (Nagel believed that pulmonary stenosis was the result of the dextrocardia.) Pic and Alaux contended that this type of dextrocardia appeared late in fetal life and was the result of associated anomalies, and that uncomplicated cases could not be congenital. Fetal endocarditis (Pal), pleuropericardial adhesions (Cipriani, Steiner, Kuchenmeister, Walther) and intra-uterine traumatism (Aperte, Laubry and Pezzi) have been incriminated as causing the simple type of dextrocardia.

In summary, it may be said that the dextrocardia with inversion is teratogenetic in origin, occurring in the first two weeks of embryonic life and the associated malformations being secondary to the anatomically deranged portions of the cardiac complex. Dextrocardia with normal relationship of the chambers is a result of certain unknown mechanical factors or transposition of the great vessels, in which case the anomaly occurs in the sixth week, or later, of embryologic development. The malformations associated with this type of dextrocardia may be necessary factors in the cause of the anomaly or the result of the same underlying etiologic factor.

## ANATOMY

In anatomic consideration of a case of isolated dextrocardia, two factors are of primary importance; first, that the transposition of the heart is not part of a general heterotaxia, and second, its inner architecture.

The so-called "ideal" mirror-image dextrocardia is attained only as part of a total situs inversus. The statement of Laubry and Pezzi that even in total situs inversus complete mirror-image dextrocardia does not exist, the great vessels not sharing in the mirror-image of the normal, the aorta lying anteriorly and on the right and the pulmonary artery lying posteriorly and on the left, rests on a confusion with the

isolated mirror-picture type of dextrocardia. Except for the position of the great vessels, the isolated mirror-picture dextrocardia may at least theoretically be virtually identical with that of total situs inversus. The axis of the heart then runs from above on the left downward to the right and anteriorly with the apex comprised of the right arterial ventricle pointing to the right (in complicated cases the apex is formed by the right ventricle transposed to the left). The right arterial ventricle contains a bicuspid valve and gives rise to the aorta which contrary to its normal left and posterior position passes to the right and forward and after deviation to the left curves on itself back to the right side and crosses the right bronchus (right aortic arch) or as frequently the left bronchus (Rösler) but only rarely descends along the right side of the vertebral column. Most commonly, after crossing the right or left bronchi, it descends along the left of the vertebral column. The anterior aspect of the heart is formed by the left venous ventricle which lies under the sternum, possesses a tricuspid valve that discharges blood into the pulmonary artery, and therefore represents the normal right ventricle. The superior and inferior venae cavae run on the left of the vertebral column and empty into the left venous auricle.

To date, however, an "ideal" mirror-image isolated dextrocardia has never been observed anatomically (Bard, Pic and Alaux, Stone, Paltauf, Nagel, Mandelstamm and Reinberg, Laubry and Pezzi). Rösler further maintained that no case exists at present with complete inversion of all the chambers of the heart. In addition to the aforementioned nonparticipation of the vessels in the mirror-image dextrocardia, cardiovascular lesions or inversions of individual segments of the cardiac complex occur. Among Rösler's 24 cases with anatomic study, there was no case with situs inversus and normal origin of vessels and there were in the literature 7 cases with abnormal origin of the blood vessels (Breschet; Reddingius; Lochte; Baumgarth; Wenner, Ratner, Abbott, Beattie; Rösler, Spitzer). Of this group an equal number of cases showed defective, or absent, septums. In at least half the cases there were changes in the pulmonary orifice. The aortic arch was found on the right as often as on the left. There was isolated inversion of the ventricular region four times (Lochte; Wenner; Ratner, Abbott; Rösler, Spitzer), of the pulmonary or caval veins, partial, twice (Breschet; Ratner, Abbott) and complete, twice (Reddingius, Baumgarth). The nearest approach to the realization of a mirror-image isolated dextrocardia is found in Graanboom's case, in which, however, a tricuspid valve was found in the right arterial ventricle, a mitral valve in the left, venous, side of the heart and the origin of the aorta on the right side and anterior to the pulmonary artery.

When isolated inversions of portions of the heart, such as the great vessels, the auricles, the valves or ventricles occur accompanied by grave anomalies of the internal structures of the heart, it is sometimes difficult to identify the arterial and venous ventricles. The determination of the respective chambers is aided by several criteria: the position of the libus foramen ovale in the right auricle, the ostia of the coronary arteries in relation to the semilunar valves (in hypoplasia of the aorta one coronary artery may arise in relation to the origin of the pulmonary artery but not both arteries), the separation of the aortic flap of the mitral from the interventricular septum by the aortic outflow tract and the direct adherence of the posterior flap of the tricuspid valve to the septal wall.

The great majority of cases of isolated dextrocardia belong anatomically to the second type with normal relationship of the chambers of the heart. The greater mass of the heart lies to the right of the median line (as in the early embryonic state), its right border projecting somewhat below the left (as in the embryo), the right venous ventricle comprising the apex (Nagel's analysis of 5 anatomic cases). In this type, also, the aorta should arise as normally, from the left ventricle, but actually it does this in only a few cases (Löwenthal; Lucchi; Pal; Bahn, Pol). In these few cases the septums are usually closed. The heart has pivoted around the vertebral column at an angle of 90 degrees with a slight change in the axis of the heart and with some degree of torsion of the great vessels. Kundrat, Nagel and others attribute the malformation of the heart and anomalies of the great vessels to this torsion. I would designate this type of dextrocardia as dextrotorsio. Of 25 cases of this type (19 of which were also studied clinically), only 3 (Pope, Lucchi, Wendling) were uncomplicated by malformations of heart and blood vessels. Anatomic cases of this group associated with abnormal origin of the vessels are reported by Holt, Birmingham, Grunmach, Nagel, Mautner and Löwy, Reggiani, MacCallum and Resnick, and Biedermann. Half of this number showed septal defects. The transposed vessels both arise out of the right or the left ventricles or out of reversed ventricles or in "corrected transposition" out of their respective ventricles. All the cases of this group, with possible exception of Reggiani's case (no mention), are complicated by pulmonary atresia or stenosis. Contrary to expectation, the aortic arch (verified anatomically) in this group of cases usually crosses the right bronchus (Grunmach, Nagel, Petit and Ravaut, Geissler, Duval, Mandelstamm and Reinberg, cases 7a and 9, Meyer and others).

The relationships of the great vessels in isolated dextrocardia are of unusual interest. As implied by Laubry and Pezzi, the vessels do

not take part in the mirror-image, the heart and blood vessels seeming to have undergone a complete rotation from behind forward and from left to right, the aorta, which normally lies posteriorly and on the left lies on the right and anteriorly, while the pulmonary artery is in the reverse position, constituting a "corrected transposition" (according to Laubry and Pezzi, true transportation of the vessels has occurred in total situs inversus only in the singular case described by Herxheimer).

In isolated dextrocardia, however, transposition of the vessels is relatively common. A group of cases of dextrocardia with normally related chambers may be said to be the result of transposition of the vessels and associated hypertrophy of the right ventricle (Paltauf, Lochte). In so-called "corrected transposition" in which the inversion of the chambers occurs simultaneously with transposition of the great vessels, the right side of the heart is arterial and gives off the aorta and the left side of the heart is venous and gives off the pulmonary artery. Lochte maintains that "corrected transposition" is the result of inversion of the cardiac tube. He cited 7 such cases in which auricles and viscera remained in a normal position, the ventricles alone being inverted. "Corrected transposition" may occur without dextrocardia.

In other cases, the aorta springs out of the right ventricle, which receives venous blood from the right auricle and is customarily found anterior to the pulmonary artery. The latter is placed behind the aorta and emerges from the left ventricle, which receives arterial blood from the left auricle (true transposition).

Geipel has summarized the incidence of transposition of the vessels in situs inversus as follows:

1. True transposition of the large blood vessels with transposition of the ventricles with or without situs inversus
2. Corrected transposition of the large blood vessels with transposition of the ventricles with or without situs inversus
3. Corrected transposition of large blood vessels without transposition of the ventricles with or without situs inversus

When the abdominal organs remain in a normal position, venous anomalies must ensue (Lochte and Kundrat; vide also cases of Graanboom and Grunmach). Transposition of the vessels to variable degrees occurs as a result of various unrelated simultaneous twistings of vessels and chambers, usually accompanied by auricular and ventricular septal defects necessary to provide mixing of venous and arterial blood compatible with life.

The position of the aortic arch in relation to the right bronchus (Mandelstamm and Reinberg, case 7A 29, Meyer's case and others) depends on an anomalous position of the vessel or the occasional persistence of a right fourth aortic arch (Arkin, Hammer).

CASES OF ISOLATED DEXTROCARDIA STUDIED ANATOMICALLY ONLY

1. Eschenbach,[101] 1769: Male, aged 6 years; apex of heart to right, base toward left (small portion to left of midline); great vessels inverted in respect to thoracic cavity; abdominal aorta to right of vertebral column; other organs in normal position. (The original article appeared in Latin; little else is recorded.)

2. Otto,[248] 1824: New-born child; median heart with apex pointing to right; rotation to left on long axis so that right border is anterior and left side of heart not seen; right auricle anterior; left auricle posterior; right ventricle short, one half the normal length; left ventricle of normal length forming entire apex of heart; great vessels normal; descending aorta on left side; small round septal defect; lungs normal; left smaller but has no cardiac incisure.

3. Breschet,[57] 1826: Dissection by Meckel at Foundling Hospital of Paris. Fibrous pericarditis; apex of heart to right; bilocular heart; persistent left superior vena cava in addition to normal right superior and inferior venae cavae; single large arterial trunk from ventricle crossing to right side of vertebral column; vestige of tricuspid valve; single ventricle communicates with auricles and aorta by two orifices; aortic valve normal; pulmonary artery does not enter ventricle; situated to the left and behind the aorta; liver, stomach, portal vein and intestinal tract normal; spleen absent; spina bifida; large thymus; lungs, three lobes each.

4. Pope,[264] 1882: Anterior flap of mitral valve adherent to endocardium with some thickening; arch of aorta in central thorax; descending aorta to left of vertebral column; branches in normal relationship; heart otherwise normal; gray hepatization of lungs; right, three lobes, larger than left; left, two lobes; abdominal organs in normal position.

5 and 6. Boerhaave[50]: Two doubtful cases; incomplete data.

Case 1, male executed prisoner; all viscera in normal position except heart, the apex of which pointed to the right.

Case 2, female executed prisoner; the so-called right chamber of the heart on the left and the left vice versa.

7. Northrup,[245] 1888: Female infant, 31 days old; cyanosis; heart inclined to right side; bilocular heart; single artery, the aorta; rudimentary septal ridge; pulmonary artery, a fibrous cord; superior vena cava on left of aorta; aorta on left of vertebral column; absence of pulmonary veins; absent mitral orifice; aortic orifice valve and tricuspid auriculoventricular valve; anomalous abdominal veins; left lobe of lung, two lobes; abdominal organs in normal position by inference of text.

8. Kundrat,[189] 1888: Female, 4 weeks old; cyanotic at birth; trilocular heart (two auricles); aorta anteriorly from giant venous ventricle; pulmonary artery posteriorly from small arterial ventricle; liver normal in size and position but left lobe greater than right; gallbladder more to the left than usual; stomach normal; spleen absent; duodneum double sling; anomalous course of portal vein.

9. Reddingius,[273] 1889 and Graanboom,[136] 1881: Icterus; ascites; pulmonary infarction; hemothorax (right); left serofibrinous pleurisy; apex of heart formed by both ventricles; aorta, normal course and branches; superior vena cava on left; pulmonary artery posterior to aorta; right ventricle anterior; left, posterior; aortic lumen narrow; tricuspid valve in right arterial ventricle; mitral valve in left venous ventricle; inversion of ventricles with corrected transposed vessels; not mirror-image heart; left lung, two lobes.

10. Holt,[163] 1890: Death from pleuropneumonia; trilocular heart biatriatum; septal ridge gives rudimentary left ventricle and major right ventricle (three fourths of heart); tricuspid, mitral and pulmonary orifices normal in right ventricle; aorta from common cavity; stenosis of orifice of pulmonary artery; aorta and branches normal; right auricle in normal position, larger than left; foramen ovale patent; chambers in normal position; cardiac incisure at left middle lobe.

11. Grunmach,[146] 1890: Death from tuberculosis; pleuritis, adherent to pericardium but not responsible for displacement; right ventricle forms round apex, larger than left (which does not reach apex); right ventricle and auricle hypertrophied and dilated, contains tricuspid valve; persistent foramen ovale; pulmonary conus stenosis; absent pulmonary valve; ventricular septum defect; aorta from left ventricle; right aortic arch behind esophagus (note error in illustration); no transposition of vessels or chambers.

12. Birmingham,[48] 1892: Pulmonary tuberculosis, especially of left lung; apex of heart formed by tip of right ventricle; anterior surface formed by both ventricles equally; aorta and pulmonary artery from right ventricle; persistent right aortic arch; ventricular and auricular septal defects; persistent left superior vena cava; no auricular appendage to right of aorta; pulmonary artery posterior and to the right of the aorta, stenosed, anomalous valve; ventricular cavities normal; mitral valve in left ventricle; transposed aorta; abdominal organs normal.

13. Lochte,[207] 1894: Male, aged 46; died of cardiac failure; atherosclerosis; chronic myocarditis; apex formed by right ventricle; anterior surface of heart formed by small right ventricle and large left ventricle; aorta to left and anterior; pulmonary artery posterior; bicuspid valve in right ventricle, giving rise to pulmonary artery; tricuspid valve in left ventricle giving rise to aorta; minute ventricle septal defect; auricles and ventricles not transposed; auriculoventricular valves transposed; corrected transposition of vessels; lungs not transposed.

14. Dalton,[90] 1898: Short clinical note. Male, aged 15 years; splenomegalia; liver on right side; death due to embolism; abdominal organs not mentioned at necropsy; right lung, two lobes; pulmonary artery more exposed than usual; persistent left superior vena cava; mitral endocarditis; apex of heart beneath right sixth rib, 2½ inches from midsternum.

15. Löwenthal,[208] 1900: Apex formed by right ventricle; left ventricle very small; right ventricle larger and thicker walled; ventricular septal defect; pulmonary artery absent; ductus botalli takes place of pulmonary artery, forms arterial trunk; superior vena cava on right; ventricles in normal relationship; abdominal organs normal.

16. Baumgarth,[34] 1902: Left lung, four lobes; single auricle receives two superior venae cavae; four pulmonary veins, and inferior vena cava; externally auricles appear reversed; primitive interventricular communication; right ventricle wide and strong; aorta from left ventricle; rudimentary stump of pulmonary artery in corrected transposition; patent ductus botalli; branches of aorta in normal relationship; cor biloculare with normal relationship of chambers; corrected transposition of vessels.

17. Lucchi,[210] 1902: No anomaly of great vessels or auricles; dilatation of aortic arch; calcification of aortic valve; dilatation of left and right ventricles; no incisure of left lung; chronic passive congestion of normally situated abdominal organs.

18. Wendling,[351] 1903: Dilated aorta; liver enlarged; normal position of abdominal organs; heart enlarged; valves normal; normal relationship of cham-

bers; apparently a normal heart; obvious postmortem rotation of apex to left; lobes of lung normal; pulmonary tuberculosis.

19. Wright and Drake,[366] 1903: Single large aorta-like vessel (bilocular heart) from superior and anterior parts of ventricle, curves like aorta; rudimentary auricular and ventricular septums; single valve between auricle and ventricle; more like bicuspid than tricuspid; normal position of abdominal organs.

20. Wenner,[352] 1909: Case 9, female, aged 10½ years; cor monoventriculare biatriatum; transposition of arterial vessels; aorta anterior, pulmonary artery stenosed, posterior, both orginating from right half of heart; apex points to right in right midaxillary line at level of eighth rib; mitral valve on right, tricuspid valve on left; persistent left superior vena cava as well as normal right; no arterial outlet to left chamber; three semilunar cusps in aorta, only two in pulmonary artery; anomalous position of atria, right huge, left small; aorta gives off branches as usual and follows usual course to left of vertebral column; abdominal organs not mentioned specifically but text infers normal position.

21. Pal,[251] and Gruss,[147] 1888, 1907, 1919: Female, aged 49 years, died of meningitis; deformity of chest; right lung adherent, three lobes; heart free; left chambers enlarged; right auricle more posterior than usual; aorta from left ventricle which is thicker than right; pulmonary artery from right ventricle; mitral valve normal; aortic valve calcareous, stenosed; great vessels normal; chambers in normal relationship; aortic stenosis, due to fetal endocarditis; abdominal organs normal.

22. Nagel,[239] 1909: Apex formed by right posterior, poorly developed ventricle; auricular septal defect; absent septum membranaceum; pulmonary artery from right ventricle; aorta from left ventricle which has bicuspid valve; pulmonary conus and ostium absent; aorta arises on left, anterior to pulmonary artery, runs to right behind esophagus, descends on left of vertebral column; inferior and superior venae cavae on right of vertebral column; three lobes in both lungs.

23. Foggie,[114] 1910: Heart enlarged; only right auricular appendage present; mitral and tricuspid valves incompetent; right ventricle forms greater part of anterior aspect of heart; cor triloculare biventriculare; liver in normal position.

24. Campergue,[66] 1912: Died with vomiting and dyspnea; congestion of lungs; liver and spleen normal; globular heart with apex deviated toward right border; dilated right auricle; tricuspid valve normal; hypertrophied right ventricle; left auricle receives vena cava; left ventricle gives off pulmonary artery (stenosed); aorta dilated; ventricular septal defect; transposition of vessels.

25. Morgan,[234] 1916: Female, aged 9 months; death following convulsions; lungs not inverted; liver, spleen and stomach normal; heart globular; left ventricle thick, right thin; valves normal; aortic arch exaggerated, branches in normal position; patent foramen ovale; no septal defect.

26. Mautner and Löwy,[216] 1921: All organs except heart in normal position; hypertrophied globular heart; apex formed by right ventricle; normal arch over left bronchus; pulmonary artery covered by aorta; cor triloculare biatriatum; right ventricle larger than left; mitral valve normal in left auriculoventricular ostium; pulmonary artery stenosed; transposition of aorta.

27. Ratner, Abbott and Beattie,[272] 1921: Female, aged 17 days; heart enlarged; apex broad, formed by both ventricles; globular in shape; right pleural transudate; auricles normal; transposition of ventricles and great vessels; right (systemic) ventricle smaller than left; tricuspid valve on left, mitral on right; ventricular septum entire; auricular septum absent (cor triloculare biventriculare); ascending

aorta from right ventricle to left; arch and descending on right; patent ductus arteriosus; aortic isthmus stenosis; right pulmonary veins into right part of common auricle; superior vena cava into persistent omphalomesenteric bay.

28. Plumier-Clermont,[260] 1924: Very small right ventricle; septal defect; riding aorta crossing right bronchus; one auricle receiving right and left venae cavae and pulmonary veins; stenosis of pulmonary artery; auriculoventricular valves normal; death from pulmonary tuberculosis.

29. Reggiani,[274] 1925: Female, aged 2½ months; cor triloculare biatriatum; apex formed by both ventricles; auricular septal defects; left side of heart with four-leaved auriculoventricular valve; aorta and pulmonary artery from right side of heart; aorta anterior to pulmonary artery; both course to right upward; patent ductus arteriosus; two coronaries with single ostium; abnormal cardiac veins.

30. Pol[261] and Bahn,[25] 1925: Male, aged 40 years; atresia of aorta beyond origin of subclavian artery; normal situs of vessels; cardiac incisure in right three-lobed lung; hypertrophied left ventricle; aortic endocarditis (lenta); recurrent mitral endocarditis; aortic isthmus stenosis; calcified tuberculosis of both apexes.

31. MacCallum and Resnik,[211] 1926: Cor triloculare biatriatum; patent foramen ovale; large ventricular septal defect; narrow, anterior aorta crosses left bronchus; pulmonary artery posterior and wide; mitral valve on left, tricuspid on right side; vena cavae and pulmonary veins in their normal auricles; ductus arteriosus closed.

32. Biedermann,[46] 1926: Female, aged 36 years; septal defect; pulmonary insufficiency, and stenosis, two-leaved pulmonary valve; aorta anterior and left from left ventricle; pulmonary artery posterior and right from right ventricle (corrected transposition); tricuspid valve on right side, mitral on left; aorta runs on left.

33. Garvin,[127] 1927: Short case presentation; no clinical notes; age and sex not given; one auricle, one ventricle; two pulmonary arteries arise symmetrically from the thoracic aorta; pulmonary veins empty into superior vena cava; inferior vena cava absent; congenitally absent spleen.

34. Rach,[271] 1927: Male, aged 4 months; apex formed by right ventricle; apex points to right; marked eccentric hypertrophy of right ventricle and right auricle with patent ductus arteriosus and foramen ovale; tracheal stenosis due to compression of right lung by hypertrophied heart.

35. Rösler[288] and Spitzer,[320] 1929: Male, aged 6 years; abdominal organs normal; pulmonary artery and aorta (left side) arise side by side, parallel from anterior border of junction of both ventricles; aorta crosses right bronchus; branches in reverse order; right ventricle has mitral valve; pulmonary conus atresia; smaller left ventricle has tricuspid valve, aorta and three-leaved normal valve; septal defect; ductus botalli and foramen ovale open; auricles and caval veins in normal relationship; transposition of aorta; pulmonary conus atresia; isolated inversion of ventricles and truncal regions; right-sided aortic arch.

36. Shapiro,[297] 1930: Male, aged 14 months; pulmonary tuberculosis with cavitation; ulcerative ileitis; miliary tuberculosis of both lungs; spleen absent; left lobe of liver larger; common auricle leading to incompletely divided ventricular cavity which empties by single arterial trunk; pulmonary artery absent; rudimentary ventricular septum; right ventricle insignificantly small; left large, forms apex; large bicuspid auriculoventricular leaflet; single larger arterial vessel with three semilunar cusps; detorsion defect of truncus arteriosus with reversal of coronary arteries.

CLASSIFICATION

A practical classification by Mandelstamm and Reinberg of cases of dextrocardia in its broader sense into four main types (type I, as found in total situs inversus; type II, isolated dextrocardia with mirror-image arrangement of chambers; type III, isolated dextrocardia with normal relationship of chambers; type IV, acquired dextrocardia) is criticized by Rösler as not being fully applicable to cases as verified anatomically. Rösler has enlarged on this classification from the point of view of his definition of "Rechtslage" of the heart, including cases of congenital dextroversion consistent with anatomic findings of proved cases.

The classification I propose for dextrocardia in its strict sense is simple, practical and faithful to the anatomic variations observed, or possible:

I. According to degree of heterotaxia
   - A. Nonisolated, occurring as part of a complete situs inversus
   - B. Isolated, heart alone transposed
   - C. Partial heterotaxia-dextrocardia associated with transposition of some other organ or portions of the vascular system

II. According to the arrangement of the chambers and great vessels
   - A. With normal arrangement of the chambers
     1. Arch of aorta crossing left bronchus
     2. Arch of aorta crossing right bronchus
     3. Persistent right aortic arch
     4. Transposition of the great vessels
     5. "Corrected transposition" of the great vessels
   - B. With mirror-picture arrangement of chambers
     1-5. As under A.

III. According to the presence or absence of complications
   - A. Uncomplicated, not associated with congenital malformation or disease
   - B. Complicated
     1. Atresia or stenosis of pulmonary and aortic orifices, or pulmonary conus
     2. Septal defects, auricular and ventricular
     3. Anomalies of number of chambers of heart, cor biloculare and triloculare
     4. Venous anomalies
     5. Anomaly of valve ostia, position, number and cusps
     6. Patent foramen ovale and ductus botalli

In all instances the apex of the heart lies to the right, and the axis is directed from the left above downward to the right. The mediastinum is in the midline, except for slight deviation of the trachea, esophagus and great veins. The ventricle constituting the apex of the heart is too variable anatomically to permit clinical classification. Since most

cases encountered thus far do not belong to any single clearcut group, in classifying any particular case it is necessary to designate the various key numbers and subgroups of the classification for a complete description of the case. For the clinical application of such a scheme in cases not verified by necropsy, roentgenographic and electrocardiographic observations are essential.

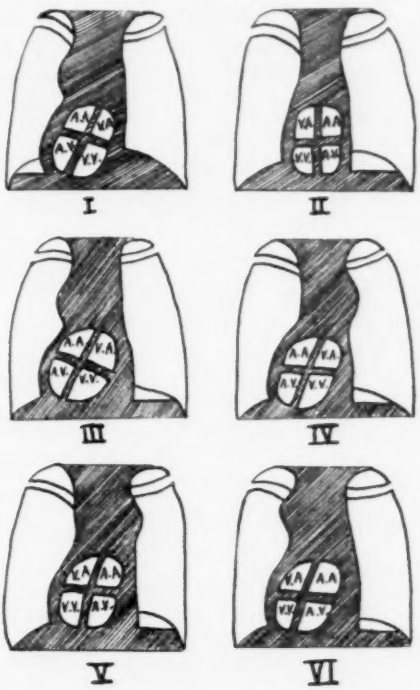


Fig. 7.—Composite schematic representation of the anatomic and roentgenographic types and variations of isolated congenital dextrocardia; *I*, mirror-image dextrocardia as found in complete situs inversus; stomach transposed also; *II*, mesocardia with apex to right side; *III*, mirror-image isolated dextrocardia with right aortic arch; *IV*, mirror-image isolated dextrocardia with left aortic arch; *V*, isolated dextrocardia with normally related chambers and left aortic arch; *VI*, isolated dextrocardia with normally related chambers and right aortic arch. The right aortic arch crosses the right bronchus and may descend on the left or right of the vertebral column. With a persistent right aortic arch, the aorta crosses behind the esophagus to descend on the left of the vertebral column.

In figure 7, the types and variations of isolated dextrocardia are represented schematically.

## CLINICAL OBSERVATIONS BASED ON CASES REPORTED IN THE LITERATURE

Cases of isolated dextrocardia complicated by gross malformations are recognized at birth or early in life by the classic signs of congenital cardiac disease. Uncomplicated cases or cases with minor malformations, on the other hand, are only casually discovered by the patient by an exaggerated pulsation in the right side of the chest, by a subjective sensation of a surging feeling or palpitation in the right side of the chest, by the clinician in the course of a routine physical examination in civilian or military life or by the pathologist at necropsy.

The analysis of the cases reported in the literature, including the two personal cases, is based on a study of:

I. 10 cases studied by necropsy only
II. 26 cases studied by necropsy and also clinically
III. 125 cases studied clinically only.

These cases are here enumerated in their respective groups, chronologically with a record of year, age, sex and roentgenogram and electrocardiogram if taken.

I. Cases studied by necropsy only:

(1) Eschenbach,[101] 1769, male, 6 years; (2) Otto,[248] 1824, new-born child; (3) Breschet,[57] 1826; (4 and 5) Boerhaave,[50] male and female adults; (6) Northrup,[245] 1888, female, 31 days; (7) Kundrat,[189] 1888, female, 4 weeks; (8) Dalton,[90] 1898, male, 15 years; (9) Wenner,[352] 1909, female, 10½ years; (10) Garvin,[127] 1927, age and sex?

II. Cases studied by necropsy and also clinically:

(1) Pope,[264] 1882, male, 41 years; (2) Reddingius,[273] and Graanboom,[136] 1889, 1891, male, 33 years; (3) Holt,[163] 1890, male, 15 months; (4) Grunmach,[146] 1890, male, 15 years; (5) Birmingham,[48] 1892, female, 20 years; (6) Lochte,[207] 1894, male, 46 years; (7) Löwenthal,[208] 1900, female, 10 months; (8) Baumgarth,[34] 1902, sex ?, 11 months; (9) Lucchi,[210] 1902, male, 63 years; (10) Wendling,[351] 1903, male, 43 years; (11) Wright and Drake,[366] 1903, male, 10 months; (12) Pal[251] and Gruss,[147] 1909, 1888, female, 49 years, roentgenogram; (13) Nagel,[239] 1909, female, 1 month, roentgenogram; (14) Foggie,[114] 1910, male, 2 10/12 years, roentgenogram; (15) Campergue,[66] 1912, male, 8 years; (16) Morgan,[234] 1916, female, 9 months, roentgenogram; (17) Mautner and Löwy,[216] 1921, male, 5 years, roentgenogram; (18) Ratner, Abbott and Beattie,[272] 1921, female, 17 days; (10) Plumier-Clermont,[260] 1924, sex ?, 14 months, electrocardiogram; (20) Reggiani,[274] 1925, female, 2½ months; (21) Pol[261] and Bahn,[25] 1925, male, 40 years, roentgenogram, electrocardiogram; (22) MacCallum and Resnik,[211] 1926, sex ?, 10 weeks, electrocardiogram; (23) Biedermann,[46] 1926, female, 36 years, roentgenogram, electrocardiogram; (24) Rach,[271] 1927, male, 4 months, roentgenogram, electrocardiogram; (25) Rösler[288] and Spitzer,[320] 1929, 1930, male, 6 years, roentgenogram, electrocardiogram; (26) Shapiro,[297] 1930, male, 14 months.

III. Cases studied clinically only:

(1) Jasinski,[167] 1861, male, 25 years; (2) Mosler,[236] 1866, male, 20 years; (3) Schroetter,[305] 1870, male, 32 years; (4) Bienfait,[47] 1873, age and sex ?; (5)

Accolas,[5] 1875, male, 52 years; (6) Ziemssen,[369] 1876, male, 28 years; (7) Mosler,[236] Falck,[103] 1877, female, 36 years; (8) Leichtenstern,[197] Wehn,[347] his case 2, 1880, male, 19 years; (9) Henoch,[154] 1880, female, 11 years; (10) Bramwell,[55] 1881, male, 39 years; (11) Theocare,[332] 1881, male, 54 years; (12) Wehn,[347] case 1, 1882, male, 27 years; (13) Mayerhofer,[217] 1883, male, 30 years; (14) Van Zant,[368] 1884, male, 31 years; (15) Süssmann,[330] 1887, male, 15 years; (16) Schroetter,[305] 1887, male, 22 years; (17) Anselmi,[16] 1888, male, 20 years; (18) Michel,[224] 1888, male, 22 years; (19) Grünfeld,[145] 1889, female, 44 years; (20) Wilks and Moxon,[359] 1889, female, 3 years; (21) Adie,[7] 1890, female, 25 years; (22) Arnaud,[17] 1891, male, 32 years; (23) Becker,[38] 1891, male, 25 years; (24) Schott,[304] 1891, male, 46 years; (25) Hawkins,[150] 1891, male, 12 years; (26) Bard,[29] 1892, female, 16 years; (27) Carmichael,[71] 1893, male, 7 years; (28) Storen,[328] 1894, male, age ?; (29) Schroetter,[305] 1894, male, 21 years; (30) Gingeot-Bard,[30] Petit and Ravaut,[259] 1895, 1897, 1898, male, 30 years; (31) Sobierajczyk,[319] Vehsemeyer,[342] 1896, 1897, male, 15 years, roentgenogram; (32) MacLennan,[212] 1869, male, 15 years; (33) Gerrard,[132] 1896, female, 26 years; (34) Berks,[42] 1896, male, 3½ years; (35) Bramwell,[56] 1896, female, 5 years; (36) Middleton,[225] 1898, male, 38 years; (37) Senator,[310] 1899, male, 6 years, roentgenogram; (38) Leo,[199] 1899, male, 8 years, roentgenogram; (39) Angyán,[15] 1899, female, 21 years, roentgenogram; (40) Bonheim,[51] 1900, male, 7 years, roentgenogram; (41) Crispino,[85] 1900, female, 55 years, roentgenogram; (42), Schmilinsky,[302] 1900, female, 9 years, roentgenogram; (43) Chapman,[77] 1900, male, 40 years; (44) Frommer,[121] 1900, female, 52 years; (45) Monks,[233] 1901, male, 28 years; (46) Gossage,[135] 1901, female, 46 years; (47) Ziemssen and Rieder,[370] 1902, male, 16 years, roentgenogram; (48) Darnall,[91] 1902, female, 69 years; (49) Wagner,[345] 1902, male, 23 years, roentgenogram; (50) Flatau,[111] 1903, female, 37 years; (51) Parkinson,[254] 1903, male, 6 years; (52) Benfey,[39] 1903, male, 6 years; (53) McIver,[219] 1905, male, 32 years; (54) Quadrone,[270] 1905, male, 25 years, roentgenogram; (55) Hochsinger,[158] 1906, sex? 7 months, roentgenogram; (56) Sheffield,[314] 1906, female, 8 years, roentgenogram; (57) Neumann,[241] 1906, male, 20 years, roentgenogram; (58) Aufdermauer,[21] case 1, 1907, male, 50 years; (59) Aufdermauer, case 6, male, 30 years; (60) Aufdermauer, case 7, female, 76 years, roentgenogram; (61) Doolittle,[94] 1907, male, 41 years; (62) Tate,[331] 1907, male, adult, roentgenogram; (63) Hawthorne,[151] 1907, male, 11 years; (64) Scandola,[296] 1909, male, 40 years; (65) Carpenter, [72] 1909, sex?, 5 years; (66) Cautley,[75] 1909, male, 7 years; (67) Whyte,[357] 1910, female, between 5 and 10 years; (68) Stoerk,[323] 1911, male, 11 years, electrocardiogram; (69) Geissler,[130] 1911, male, adult; (70) Vanderwelde,[340] Cantineau-Vandeput,[338] 1911, 1912, male, 14 years, roentgenogram; (71) Brooks,[60] 1911, female, 13 years; (72) Culcer-Petresco,[86] 1912, female, 9 years, roentgenogram; (73) Giovannini,[133] 1913, female, 67 years, roentgenogram; (74) Tison,[333] 1914, sex?, 4 years, roentgenogram; (75) Botteri,[53] 1914, female, 36 years, roentgenogram; (76) Moffett and Neuhof,[229] 1915, male, 3½ years, electrocardiogram; (77) Martin,[214] 1915, male, 19 years, roentgenogram; (78) Stolkind,[325] 1816, male, 52 years, roentgenogram; (79) Aitken,[10] 1917, male, 17 years, roentgenogram; (80) Clerc and Bobrie,[80] 1917, male, 29 years, roentgenogram; (81) Boruttau and Stadelmann,[52] 1917, age and sex?, roentgenogram, electrocardiogram; (82) Indemnas,[166] 1918, male, 25 years, roentgenogram; (83) Duval,[97] 1919, male, adult, roentgenogram; (84) Parsons-Smith,[255] case 3, 1919, male, 31 years; (85) Parsons-Smith, case 4, male, 27 years; (86) Hesselgren,[156] 1919, sex?, 14 days, roentgenogram; (87) Weinberger,[349] case 1, 1919, male, 47 years, roentgenogram, electrocardiogram; (88) Weinberger, case 2, female, 21 years, roentgenogram, electrocardiogram; (89)

Vaquez and Donzelot,[341] case 2, 1920, male, 21 years, roentgenogram, electrocardiogram; (90) Reinberg, same as case 5 of Mandelstamm and Reinberg,[213] 1922, male, 35 years, roentgenogram, electrocardiogram; (91) Fumaioli,[124] 1922, female, 18 months; (92) Meyer,[223] 1923, female, 17½ years, roentgenogram, electrocardiogram; (93) Curschmann,[58] 1924, male, 40 years, electrocardiogram; (94) Jones,[169] case 3, 1924, female, 35 years, roentgenogram, electrocardiogram; (95) Jones, case 4, male, 27 years, roentgenogram, electrocardiogram; (96) Fulchiero and Bruno,[123] 1924, male, 22 years, roentgenogram, electrocardiogram; (94) Augey,[22] 1924-1925, age?, sex?; (98) Gorter,[134] case 1, 1925, sex?, 4 months, roentgenogram, electrocardiogram; (99) Gorter, case 2, sex?, 2 years, electrocardiogram; (100) Gorter, case 4, female, 7 years, roentgenogram, electrocardiogram; (101) Gorter, case 5, sex?, 4 months; (102) Capon and Chamberlain,[69] 1925, female, 26 months, roentgenogram, electrocardiogram; (103) LeWald,[202] 1925, female, 24 years, roentgenogram, electrocardiogram; (104) Ponzio,[263] 1926, sex?, age?, roentgenogram; (105) Gautier and Coeytaux,[128] 1926, male, 18 months, roentgenogram, electrocardiogram; (106) Lenk,[198] 1926, female, 14 years, roentgenogram, electrocardiogram; (107) Colvin,[62] 1926, female, 28 years, roentgenogram, electrocardiogram, (108) Prendergrass,[269] 1927, sex?, age?, roentgenogram; (109) Aimé,[9] 1927, sex?, age?, roentgenogram; (110) Krestin,[184] 1927, female, 30 years, roentgenogram, electrocardiogram; (111) Milani,[226] 1928, female, 27 years, roentgenogram; (112) Loben,[206] 1928, male, 22 years, roentgenogram; (113) Mandelstamm and Reinberg,[213] case 6, 1928, male, 36 years, roentgenogram, electrocardiogram; (114) Mandelstamm and Reinberg, case 7, sex and age?, roentgenogram; (115) Mandelstamm and Reinberg, case 7a, female, 7 years, roentgenogram, electrocardiogram; (116) Mandelstamm and Reinberg, case 7b, sex?, 15 years, roentgenogram, electrocardiogram; (117) Mandelstamm and Reinberg, case 9, female, 14 years, roentgenogram, electrocardiogram; (118) Strothmann,[329] 1929, male, 9 years, roentgenogram, electrocardiogram; (119) Rösler,[288] case 1 (see Rösler and Spitzer's case with necropsy); case 2, 1930, male, 17 years, roentgenogram, electrocardiogram; (120) Rösler, case 3, female, 11 years, roentgenogram, electrocardiogram; (121) Rösler, case 4, male, 33 years, roentgenogram, electrocardiogram; (122) Rösler, case 5, female, 36 years, roentgenogram, electrocardiogram; (123) Rösler, case 7, male, 27 years, roentgenogram; (124) Lichtman, case 1, 1931, female, 21 years, roentgenogram, electrocardiogram; (125) Lichtman, case 2, male, 46 years, roentgenogram, electrocardiogram.

Analysis of the cases collected from the literature, totaling 161 (including 2 personal cases), indicates that the majority occur in males (87 and 51) and that there is a greater incidence in the first three decades of life. In the entire series only 3 cases proved clinically and anatomically to be uncomplicated by a congenital cardiac malformation (Pope, Lucchi, Wendling), while 45 (of 150 cases) were frankly complicated with clinical symptoms and signs of congenital cardiac disease. Rösler denied the existence of an uncomplicated case. The nature of the malformations in these cases is listed as follows:

Pulmonary stenosis and septal defect:

Clinical (7 cases): Wehn, case 2; Hawkins; Fumaioli; Strothmann; Wardrop, Griffith?; Bonheim?; Lenk?

Necropsy (4 cases): Baumgarth, pulmonary artery absent; Campergue; Mautner and Löwy; Biedermann.

Pulmonary stenosis, ventricular septal defect, patent foramen ovale or auricular septum defect:
Necropsy (5 cases): Holt; Grunmach; Birmingham; Nagel; pulmonary artery absent, Plumier-Clermont.
Pulmonary stenosis, ventricular septal defect and patent ductus arteriosus:
Clinical (2 cases): Berks, Moffett and Neuhof; with patent foramen ovale.
Necropsy (1 case): Rösler, Spitzer; with patent foramen ovale.
Disease of pulmonary artery alone:
Clinical (4 cases): Mayershofer?; Adie; Gorter, cases 1? and 4.
Auricular septal defect or patent foramen ovale and ventricular septal defect:
Clinical (1 case): Lichtman, case 2?.
Necropsy (3 cases): MacCallum and Resnik; Wright and Drake; Shapiro; pulmonary artery absent.
Septal defect alone:
Clinical (8 cases): Bramwell?; Middleton?; Hochsinger; Culcer-Petresco; Parsons-Smith, case 4; Fulchiero and Bruno; Milani; Lichtman, case 1
Necropsy (1 case): Lochte.
Patent ductus arteriosus, with auricular and ventricular septal defects:
Necropsy (1 case): Reggiani.
Patent ductus arteriosus, auricular septal defect, aortic stenosis:
Necropsy (1 case): Ratner; Abbott and Beattie.
Patent ductus arteriosus and foramen ovale:
Clinical (1 case): Weinberger, case 2.
Aortic stenosis:
Clinical (1 case): Curschmann.
Necropsy (2 cases): Pal, Gruss; Pol, Bahn.
Patent foramen ovale or auricular septal defect alone:
Necropsy (1 case): Foggie.

In seven cases of the series there was a history of acute articular rheumatism (Grünfeld; Gerrard; Gossage; Parkinson; McIver; Weinberger, case 1; Rösler, case 4); in fourteen, acquired valvular disease (Theocard; Bard; Angyan [?]; Quadrone [?]; Hawthorne; Geissler, case 5; Jones, case 4; Krestin; Pope; Graanboom; Lucchi; Pol, Bahn; Aufdermauer, case 7; Weinberger, case 1); in four, signs of cardiac hypertrophy alone (Vehsemeyer, Mosler, Bienfait, Arnaud), and in eight, only symptoms of cardiac trouble (Accolas; Schott; Gingeot, Bard, Petit and Ravaut; Darnall; Stoerk, Giovannini; Meyer; Jones, case 3). Forty-two cases showed definitely normal heart sounds and 6 cases that came to necropsy had shown normal sounds (Löwenthal; Baumgarth; Wendling; Wright and Drake; Rösler, Spitzer; Shapiro). A history or evidence of extracardiac intrathoracic disease (pleurisy, pneumonia, pulmonary tuberculosis, pericarditis) was present in 32 cases and thoracic asymmetry or deformity of scoliosis of the dorsal spine in 23 cases.

In 10 cases in which the relative position of the testicles was noted only in 1 case was the right lower (Scandola). In 15 cases in which

TABLE 1.—*Cases of Isolated Congenital Dextrocardia Studied Clinically, by Roentgenogram, Electrocardiogram and by Necropsy*

| No. | Author and Date | Sex and Age | Family History; Cardiac Twins | Right or Left-Handed | Testicle Lower | Cardiac Symptoms | Abnormal Cardiac Signs | Roentgenogram: Aorta: Arch | Roentgenogram: Aorta: Descending | Roentgenogram: Abdominal Organs | Roentgenogram: Cardiac Shadow | Roentgenogram: Diaphragm Leaf Lower | Roentgenogram: Lung Fields | Electrocardiogram: P I | Electrocardiogram: P II | Electrocardiogram: P III | Electrocardiogram: QRS I | Electrocardiogram: QRS II | Electrocardiogram: QRS III | Electrocardiogram: T I | Electrocardiogram: T II | Electrocardiogram: T III | Comment | Necropsy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Plumier-Clermont,[269] 1924 | ? 14 mos. | 0 | 0 | .. | Cyanosis; clubbing; polycythemia; cardiac malformation, Fallot type | Systolic murmur at base | Right bronchus (post mortem only) | ? | ..... | Right | ? | ? | .. | .. | .. | .. | .. | .. | — | .. | .. | No illustrations or other data | Very small right ventricle; septum defect; riding aorta crossing right bronchus; one auricle receiving right and left vena cavae and pulmonary veins; pulmonary artery stenosed; valves normal; death from pulmonary tuberculosis |
| 2 | Pol [25] and Bahn,[261] 1925 | Male 40 yrs. | Mother died of heart disease | 0 | .. | Dyspnea, 4 weeks; slight cyanosis and clubbing | Systolic murmur over valvular areas | Left (first oblique view) | Left | Stomach normal ($CO_2$ gas); spleen and liver normal | Right | ? | ? | + | + | + | + | + | + | — | — | + | T I and II considered + by Bahn; no ventricular predominance | Atresia of aorta beyond origin of subclavian; normal situs of vessels; cardiac incisure in right three-lobed lung; hypertrophy of left ventricle; aortic endocarditis (lenta); recurrent mitral endocarditis; aortic isthmus stenosis; calcified tuberculosis of both apexes |
| 3 | Biedermann,[46] 1926 | Female 36 yrs. | ..... | .. | .. | ..... | ..... | ..... | ..... | ..... | Right | Both equal level | .. | + | + | + | — | — | ? | — | — | + | ..... | Septal defect; pulmonary insufficiency and stenosis; two leafed pulmonary valve; aorta anterior and left from left ventricle; pulmonary artery posterior and right from right ventricle; corrected transposition; tricuspid on right; mitral on left; aorta runs on left of vertebral column |
| 4 | Rösler[288] and Spitzer,[320] 1929-1930 | Male 6 yrs. | Younger brother has congenital heart disease; consanguineous marriage | 0 | 0 | Morbus coeruleus; no murmurs at birth; syncope and spasms first year; cyanosis, clubbing fingers and toes; polycythemia | Heart sounds pure; no thrill; liver, three finger-breadths below right costal margin | Right bronchus | Right of vertebral column | Stomach normal | Right; transverse to slight degree; left ventricle forms apex | Right slightly lower | — | + | — | — | — | — | + | — | + | + | Sinus rhythm; no right ventricular predominance; conduction normal; T II hardly visible | Abdominal organs normal; pulmonary artery and aorta (left) arise side by side, parallel from anterior border of junction of both ventricles; aorta crosses right bronchus; branches of aorta in reverse order; right ventricle has mitral valve; pulmonary conus atresia; smaller left ventricle has tricuspid valve, aorta and three-leafed normal valve; septal defect; ductus botalli and foramen ovale open; auricles and caval veins in normal relation; transposition of aorta; pulmonary conus atresia; isolated inversion of ventricle and truncal regions; right-sided aortic arch |

dexterity was considered, left-handedness occurred in 5 (Parsons-Smith, case 4; Doolittle; Bonheim; Sobieryczyk, Vehsemeyer; Mosler, Falck).

Inversion of the chambers of the heart was claimed in 19 cases of the series:

Physical signs only (3 cases): Mosler; Sussmann; Schroetter.

Roentgenograms (2 cases): Schmilinsky; Weinberger, case 1?

Electrocardiogram (10 cases): Moffett and Neuhof; Meyer, LeWald; Gorter, case 5; Capon and Chamberlain, Moffett and Neuhof, case 9; Strothmann; Rösler, Spitzer; Rösler, case 5; Lichtman, case 1.

Necropsy (4 cases): Graanboom; Breschet; Ferrein, Eschenbach; Rösler, Spitzer.

It is of interest to note that the 3 uncomplicated cases in the series (proved by necropsy) belong to the type of dextrocardia with normally related chambers.

Significant roentgenographic and electrocardiographic features and points of diagnostic significance will be discussed under their respective headings.

In table 1 are tabulated the findings in the only 4 cases in the literature which were studied clinically, by roentgenogram, electrocardiogram and by necropsy.

*(To be concluded)*

# Book Reviews

THE DEVELOPMENT OF PHYSIOLOGICAL CHEMISTRY IN THE UNITED STATES. By RUSSELL H. CHITTENDEN. American Chemical Society, Monograph Series. Price, $6. Pp. 427. New York: The Chemical Catalog Company, Inc., 1930.

This monograph constitutes an excellent review of the major part of the graduate instruction and more important investigative work in physiologic chemistry in most of the educational and research institutes in the United States. The historical treatment in the first part of the book clearly shows the influence of European training on the earlier physiologic chemists of the United States as well as the later and rapid growth of a new school, largely through the development of separate departments of physiologic chemistry or biochemistry in the larger institutions. The author later emphasizes that the subject of physiologic chemistry should be recognized and "treated as a pure science unhampered in its growth by any form of application," that it "should have perfect freedom to progress and expand in any and all directions without regard to possible applications" and that "applications will come fast enough as the science advances." Many phases of biologic chemistry are reviewed very fairly and relatively completely, while other contributions of equal importance or prominence or equally recent and of equally long standing are rather conspicuously absent. It was, to be sure, impossible to include all American contributions to physiologic chemistry in so limited a volume, but it may be questioned whether the space now devoted to enumerating academic records of men, similar to the information given in "American Men of Science," had not been utilized more profitably and fairly for the addition of obvious omissions. The Yale influence is, of course, obvious in many instances, partly because of its real influence and secondly because of the author's years of association and interest.

AFFECTIONS DOULOUREUSES DE L'INTESTIN TERMINAL. By C. BONORINO UDAUNDO and L. V. SANGUINETTI. Price, 9 francs. Pp. 24. Paris: Gaston Doin, 1931.

The chief value of this publication is that it calls attention to the so-called functional pains in the recto-anal regions. The author contends that pain associated with conditions in the lowest colonic segments is sufficiently characteristic so that one is usually able to suspect the cause.

The anatomy of the rectum and anus is described, following which functional pains are discussed in some detail. Such pains are either lancinating or severe burning with griping, occur most frequently at night, last from ten minutes to an hour, are influenced very little by defecation, and appear in attacks with intervals of freedom. They are really neuralgias. Illustrative cases are cited. It is pointed out that functional pains may be present with some organic lesions; for example, hemorrhoids, and that surgical treatment for such a painful condition usually fails to give relief. No one satisfactory treatment is known.

Pains due to organic lesions are discussed, but this adds little to the general knowledge of these conditions.

THE INTERNATIONAL MEDICAL ANNUAL FOR 1931. Edited by CAREY F. COOMBS and A. RENDLE SHORT. Price, $6. Pp. 551. New York: William Wood & Company.

This is the forty-ninth year book, written by English and Canadian authors. The editors' purpose is to furnish a digest of the world's medical literature, critically considered and reduced to a small bulk by competent authorities. As a rule, pathology is not included in the discussions, but particular attention is called to new and improved methods of diagnosis and treatment that seem promising. Each article is signed, so that the reader may know the identity of the author. The subjects are arranged alphabetically, and ample references are given.

The Annual has an interesting introduction by the editors which outlines many of the new and important advances in medicine during the year. These are covered in greater detail in the book. A section on diseases of the teeth is included in this edition. The articles are well written, and the authors have confined themselves to matters of importance. As must be expected in such a book, minor details cannot be included, but the original articles are always referred to.

The book is valuable to any one doing general work who does not have much time for extensive reading. All branches of medicine are covered, and a wealth of material is condensed in a readable manner.

LA FOLIE ET LA GUERRE DE 1914-1918. By A. RODIET and A. FRIBOURG-BLANC. Price, 30 francs. Pp. 194. Paris: Félix Alcan, 1930.

This book represents a study of about 2,500 observations of mental disturbances arising among French troops during the World War, in an attempt to answer the following questions. 1. Are there war psychoses constituting special mental diseases differing in origin and evolution from the ordinary psychoses in times of peace? 2. Does war favor the development of the usual psychoses observed in times of peace and increase their number?

The first question is answered in the negative. The second question is answered in the affirmative, and arguments are presented to prove that the increase in number of the usual psychoses is due to exciting causes such as emotional shocks, physical misery, wounds, contusions, infections and intoxications (especially alcohol) which are augmented by the conditions of war.

GRUNDZÜGE DER NEUROCHIRURGIE. By WALTER LEHMANN. Price, 13.50 marks. Pp 197. Leipzig: Theodor Steinkopff, 1930.

In this small volume are considered in brief the operative procedures that have to do with most of the neurosurgical conditions of the central nervous system. It is obvious that in so few pages very little detail has been attained. Nevertheless, for a general surgeon the conceptions of the neurosurgeon are well expressed. That holds especially for traumatic lesions of the brain, fracture of the skull and intracranial hemorrhage. As far as the tumors themselves go, the subject matter is totally inadequate.

The author discusses surgery of the peripheral nerves of the vegetative nervous system, of painful diseases and of spastic paralysis, so that a general survey of the neurosurgical methods can be obtained from a perusal of this work. The book is highly recommended for the general surgeon. The specialist, however, will not gain much from it.

CANCER. By WILLY MEYER. Price, $7.50. Pp. 427. New York: Paul B. Hoeber, Inc., 1931.

This volume of 427 pages includes both an experimental and a clinical study of the etiology and treatment of carcinoma. There is an enormous collection of evidence of various sorts indicating the presence of alkalosis as the most important

etiologic factor, and the author's treatment is based on trying to reverse the metabolic status in the production of an acidosis.

While the reviewer would not subscribe to the acceptance of the interpretation placed on the evidence by Dr. Meyer, either clinically or experimentally, he feels that the book is worth while simply as a compilation of data and a statement of the present standing of a very controversial subject.

LES RÉACTIONS VASO-MOTRICES DU FOIE, EN CLINIQUE. By DR. ROGER GLÉNARD, Paris. Paper. Price, 30 francs. Pp. 240, with 19 illustrations. Paris: Gaston Doin, 1931.

This is another monograph of the usual type on the diagnosis and therapy of disorders of the liver, not so much disorders of hepatic function, as disorders of the size and position of the liver. Methods of palpitation, roentgen outlining, etc., are described in detail, and figures are presented. It is a useful manual for the physician familiar with the French language, but contains nothing particularly new.

## CORRECTION

In the article by Dr. Eli Moschcowitz entitled, "The Relation of Achlorhydria to Pernicious Anemia," in the August issue (ARCH. INT. MED. **48**:171, 1931), 0.21 per cent at the end of the fourth line from the bottom on page 172 and at the beginning of the sixth line from the top of page 173, referring to the incidence of achlorhydria, should read 2.1.

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